



Basic Pharmaceutical Sciences I

Learning Module

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Preface

In response to the critical shortage of pharmacy/Medical laboratory personnel in Oromia National regional state, a group of experts from universities and colleges in the region have developed an Outcome based TVET Model curriculum for Pharmacy Level II-IV programs in October, 2017 with the initiative of Oromia Regional Health Bureau.

The outcome based curriculum was developed in reference to the level based 2011 Ethiopian Occupational standard. The guiding principle in the development of the outcome based curriculum was to train Pharmacy professionals in focused, time efficient and outcome based approach, and to fill the existing pharmacy works force shortage with competent professionals.

The key features of the outcome based curriculum include: use of variety of teaching/learning methods, repeated exposure of trainees to skill laboratories, practical attachment/cooperative training and the delivery of the training in standardized learning modules (information sheets) and skill lab manual/checklists (Operation sheets).

This learning module was developed by a diverse group of experts from higher teaching institutions in Oromia region, experts from Oromia Regional health bureau, Oromia TVET, Oromia COC agency and professional associations.

This Basic Pharmaceutical Science I learning Module covers 3 unit of competencies in the level II pharmacy program. The learning module covers both theoretical and practical aspects of the competencies.

Dear Trainee, you are expected to read the information presented in the learning module, attempt all the self-check questions and perform skill activities as per the skill lab learning guide/checklist.

Acknowledgment

This Basic Pharmaceutical Science I learning module and skill lab manual for **Retail Pharmacy assisting Level II Program** was developed by experts from Universities and Colleges in Oromia National Regional State.

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1. Introduction to pharmacy

Dear trainees, at the end of this chapter, you will be able to:

-  Recognize history of pharmacy from ancient times to today
-  Define what pharmacy profession is
-  Identify the settings where pharmacy professionals work
-  Recognize the roles of pharmacy technicians

In earliest times, medicine was based in magic and religion. Ancient people believed that demons were the cause of illness and health could be restored by identifying the demon and finding a way to cast it out. Those who became most proficient in the use of drugs to treat disease were the “mediators” between this world and the spirit world, namely, the priests, shamans, holy persons, witches, and soothsayers.

However, the use of drugs to effect cures led to a profound change in both religious thought and structure. As more became known about the effects of drugs, the importance of divine intervention began to recede, and the treatment of patients effectively became a province of the priest rather than the gods whom the priest served. This process led to a growing understanding of the curative powers of natural products and a decreasing reliance on supernatural intervention and forever altered the relationship between humanity and its gods.

Early man understood that plants and other natural materials had the power to treat or relieve illness. Ancient Sumerians used about 250 natural medicines derived from plants, many of which are still used today. By simple trial and error, humans slowly discovered things in nature that helped them.

77 B.C Dioscorides, a Greek physician, wrote the *De Materia Medica*, five books that described over 600 plants and their healing properties. His work was the main influence for over sixteen hundred years. One of the remedies he described was made from the bark of a type of willow tree, the active ingredient of which was salicylic acid, the natural drug on which acetylsalicylic acid (Aspirin) is based.

Ancient cultures around the world used medicines made from natural sources, many of which contained drugs that we still use today. However, over the past two centuries, science found ways to create synthetic drugs. Some of these man-made drugs replaced natural drugs and others were for entirely new uses.

The earliest known record of the art of the pharmacist is in Babylon, the jewel of the ancient Mesopotamia, now Iran, and previously Persia. Practitioners at this time were priests, pharmacists, and physicians, all in one. The Chinese also contributed to early pharmacy. From this point forward in history, the art of crude medicine preparation and pharmacy became more refined by the Egyptians, the Greeks, and the Romans.

Pharmacy is the art and science of preparing and dispensing medications and the provision of drug-related information to the public. It involves the interpretation of prescription orders; the compounding, labeling, and dispensing of drugs and devices; drug product selection and drug utilization reviews; patient monitoring and intervention; and the provision of cognitive services related to use of medications and devices. It is a health profession that links health sciences with chemical sciences and aims to ensure the safe and effective use of pharmaceutical drugs.

The scope of pharmacy practice includes more traditional roles such as compounding and dispensing medications, and it also includes more modern services related to health care, including clinical services, reviewing medications for safety and efficacy, and providing drug information. Pharmacists, therefore, are the experts on drug therapy and are the primary health professionals who optimize use of medication for the benefit of the patients.

Pharmacists are health care professionals with specialized education and training who perform various roles to ensure optimal health outcomes for their patients through the quality use of medicines. Pharmacy technicians support the work of pharmacists and other health professionals by performing a variety of pharmacy related functions, including dispensing prescription drugs and other medical devices to patients and instructing on their use. They may also perform administrative duties in pharmaceutical practice, such as reviewing prescription requests with medication offices and insurance companies to ensure correct medications are provided and payment is received.

The field of pharmacy can generally be divided into four primary disciplines:

- Pharmacology
- Pharmaceutics
- Pharmacognosy
- pharmacy practice

The boundaries between these disciplines and with other sciences, such as biochemistry, are not always clear-cut. Often, collaborative teams from various disciplines

Pharmacognosy

The American Society of Pharamacognosy defines pharamacognosy as: “the study of the physical, chemical, biochemical and biological properties of drugs, drug substances or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources ”

Pharmacology

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes. Pharmacology can also be defined as the science of substances used to prevent, diagnose, and treat disease.

Pharmaceutics

Pharmaceutics is science concerned with the scientific and technological aspects of the design and manufacture of dosage forms. It is the science of dosage form design or preparation.

Pharmacy Practice

Pharmacy Practice is vital, since it facilitates and enables pharmacists to fully exploit their substantial knowledge and expertise. The practice of pharmacy aimed at providing and promoting the best use of drugs and other health care services and products, by patients and members of the public.

Where do pharmacy professionals work?

Areas of Pharmacy Practice

- ✚ Community Pharmacy: Community pharmacists are the health professionals most accessible to the public. They supply medicines in accordance with a prescription or, when legally permitted, sell them without a prescription
- ✚ Hospital Pharmacy: The department or service in a hospital which is under the direction of a professionally competent, legally qualified pharmacist, and from which all medications are supplied to the nursing units and other services, where special prescriptions are filled for patients in the hospital, where prescriptions are filled for ambulatory patients and out-patients, where pharmaceuticals are manufactured in bulk, where narcotic and other prescribed drugs are dispensed, where injectable preparations should be prepared and sterilized, and where professional supplies are often stocked and dispensed.
- ✚ Other areas: pharmaceutical industries, drug regulatory and supply agencies etc.

Role of pharmacy technicians in the Pharmaceutical services: pharmacy technicians are involved in all facets of drug distribution. Their responsibilities include:

- ✚ Receiving written prescriptions or requests for prescription refills from patients or their caregivers.
- ✚ Verifying that the information on the prescription is complete and accurate
- ✚ counting, weighing, measuring, and mixing the medication
- ✚ preparing prescription labels and selecting the container
- ✚ establishing and maintaining patient profiles
- ✚ ordering and stocking prescription and over-the-counter medications
- ✚ tracking and reporting errors
- ✚ prepare extemporaneous product master work sheets and labels;
- ✚ supervises small-scale compounding of aseptic pharmaceutical products;
- ✚ maintain procurement and storage of pharmaceutical products;
- ✚ maintain distribution of pharmaceutical products;
- ✚ support pharmacists by providing specific information to/for clients;
- ✚ manage implementation of Occupational Health Standard (OHS); and
- ✚ manage first-aid policy.

Assignment: List and clearly discuss the different areas where pharmacy professionals can be employed and the roles of pharmacy technicians

2. General principles of drug actions

Dear trainees, upon completion of this chapter, you will be able to:

- + Define the basic terms (pharmacology, drug, pharmacokinetics, pharmacodynamics, side effects, indication and contraindication)
- + Recognize how drug names are created and how their names can indicate usage
- + Identify the source of drugs and give example of drug for each source
- + Describe the four pharmacokinetic phases and factors that influence each phase
- + Identify commonly dispensed dosage forms
- + Compare and contrast various routes of drug administration
- + Compare and contrast agonists and antagonists, efficacy and potency
- + Describe factors that influence drug action and dosage

2.1. Definitions of basic terms

Before talking about the concepts in pharmaceutical sciences, it would be important to be familiar with the following terms.

- **Drug, Dose, dosage, pharmacokinetics, pharmacodynamics, mechanism of action, therapeutic effects, side effects (adverse effects), indications and contraindications**

What is drug?

Drug is a substance or a chemical that interact with human and/or animal body to exert its effects. In pharmacology drug is a chemical substance used for prophylactic, diagnosis and treatment of disease in man or other animals.

Dose: the quantity of drug which is sufficient to diagnose, prevent, or treat a disease.

Dosage: the schedule of dose, frequency and duration of administration.

Pharmacokinetics: is the study of the absorption, distribution, metabolism and excretion of drugs from the body. Simply put, it is the study of “**what the body does to drugs**”.

Pharmacodynamics: is the study of the biochemical and physiological effects of drugs and their mechanisms of action. It deals “**what the drug does to the body**”.

Mechanism of Action: How the drug exerts its action

Effects (therapeutic effects): The desired results of administration of a medication

Side Effects (adverse effects): Effects that are harmful and undesired, and that occur in addition to the desired therapeutic effects

Indications: The reasons for administering a medication or performing a treatment

Contra-indications: Factors that prevent the use of a medication or treatment (e.g., Allergies)

2.2. Sources of drugs

Drugs are obtained from the following sources:

- **Plants:** quinine from Cinchona (*Cinchona officinalis*), Atropine from Belladonna (*Atropa belladonna*), etc
- **Animals:** Insulin from pancreas of beef or pig, thyroxine from thyroid gland, etc
- **Minerals:** Iron, iodine, calcium, Magnesium trisilicate and aluminium hydroxide, etc
- **Microbes:** Penicillin from *Penicillium notatum* (Fungus), Streptomycin from *Streptomyces griseus*, etc
- **Synthetic:** Aspirin, Sulphonamides, Paracetamol, Chloroquine, etc
- **Semi-synthetic:** Amoxicillin, Ampicillin, etc

2.3. Drug names

A single marketed drug may have three types of names:

- a chemical name,
- a generic (nonproprietary) name, and
- a trade or brand name

A. A chemical name is a name given based on the chemical makeup (constituent) of the drug. It is almost never used to identify the drug in a clinical or marketing situation.

✚ Eg. N-(4-hydroxyphenyl) acetamide

B. A generic (nonproprietary) name is a shortened form of a chemical name listed in pharmacopeia. For example, the generic name of the above-mentioned drug (N-(4-hydroxyphenyl) acetamide) is:

✚ Acetaminophene- in United states adopted name (USAN) and

✚ Paracetamol –in Australian Approved Name (AAN) and British Approved Name (BAN)

✚ Generic names are preferable to trade names for general use

C. A trade or brand name is a name that is registered by the manufacturer and is followed by the trademark symbol. A drug may have several trade names. For example, some brand names of the above-mentioned drug, acetaminophen, are: Tylenol (USA), Panadol (UK), panodil (denmark).

2.4. Drug categories

After approval of a drug, the FDA (Food and Drug Authority) assigns the drug to one of the following categories: **Prescription, Non-prescription, and controlled substance.**

Prescription drugs: are drugs that are potentially harmful unless their use is supervised by a licensed health care provider. Prescription drugs, also called legend drugs, are the largest category of drugs. Drugs in this class are obtained only with written order (prescription) by a licensed healthcare provider.

- Prescription is a legal order for specific drug, to be dispensed to a patient by a licensed pharmacist.

Non-prescription drugs: are drugs that are designated by the FDA to be safe (if taken as directed) and obtained without a prescription. These drugs are also referred to as over-the-counter (OTC) drugs and may be purchased in a variety of settings, such as a pharmacy, drug store. OTC drugs include those given for symptoms of the common cold, headaches, constipation, diarrhea, and upset stomach.

Controlled substances: are the most carefully monitored of all drugs. These drugs have a high potential for abuse and may cause physical or psychological dependence. They are usually ordered with a special prescription paper. Prescriptions for these drugs cannot be filled more than 6 months after the prescription was written or be refilled more than five times. Controlled substances are generally classified into five schedules.

Table 2.1: Schedules of Controlled Substances

Schedule	Abuse Potential	Prescription Requirement	Examples
I(C-I)	high; no accepted medical use	no prescription permitted	heroin, LSD (lysergic acid diethylamide), marijuana, mescaline
II(C-II)	high; accepted medical use	Prescription required; no refills permitted without a new written prescription	fentanyl, methadone, methamphetamine, morphine
III(C-III)	moderate; accepted medical use	Prescription required; 5 refills permitted in 6 months	certain drugs compounded with small quantities of narcotics; also, other drugs with strong potential for abuse and certain barbiturates
IV(C-IV)	low; accepted medical use	Prescription required; 5 refills permitted in 6 months	barbital, chlordiazepoxide, diazepam, and pentazocine
V(C-V)	low; accepted medical use	no prescription required for individuals 18 or older unless quantities are greater than 4 fluid ounces.	cough syrups with codeine, diphenoxylate atropine sulfate, and kaolin/pectin/opium

2.5. Drug Dosage forms

A dosage form of a drug is the form of preparation designed for administration to the body. After development of a specific drug for its pharmacological effects, it is formulated in a form that is suitable for administration and even efficacy and for the stability of the drug itself.

Why do we need to have different dosage forms?

- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity eg. Coated tablets
- To protect the drug substance from the destructive influence of gastric acid after oral administration e.g. Enteric-coated
- To conceal the bitter, salty or offensive taste or odor of a drug substance e.g. Capsules, Flavored syrups
- To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle e.g. Suspension
- To provide clear liquid dosage forms of substances e.g. Syrups, Solutions
- To provide rate-controlled drug action e.g. Controlled-release tablets
- To provide optimal drug action from topical administration sites eg. Ointments, Creams, and transdermal patches
- To provide for insertion of a drug into one of the body's cavities (e.g. Suppositories)
- To provide placement of drugs directly in the bloodstream or body tissues (e.g. Injections)
- To provide for optimal drug action through inhalation therapy (e.g. Inhalants, Inhalation aerosols)

Composition of dosage forms

In a dosage form, the active pharmaceutical ingredient (API) is combined with the inactive pharmaceutical ingredients (additives, adjuvant, excipient) that facilitate administration of the drug. The active pharmaceutical ingredient is responsible for a drug's therapeutic effect. The inactive pharmaceutical ingredient has little or no therapeutic effect.

Direct clinical use of the active drug substances, as they are, is rare due to a number of good reasons:

- API handling can be difficult or impossible (e.g., low mg and µg doses)
- Accurate drug dosing can be difficult or impossible
- API administration can be impractical, unfeasible or not according to the therapeutic aims
- Some API can benefit from reducing the exposure to the environmental factors (light, moisture...), or they need to be chemically stabilised due to the inherent chemical instability
- API can be degraded at the site of administration (e.g., low pH in stomach)
- API may cause local irritations or injury when they are present at high concentrations at the site of administration
- API can have unpleasant organoleptic qualities (bad taste or smell which affect patient compliance)
- Administration of active substance would mean to have no chance for modification (improvement) of its Pharmacokinetic profile

Inactive pharmaceutical ingredients of a dosage form include:

- **Binders**-promote adhesion of active and inactive ingredients in the tablets
- **Diluents**-are additives used to increase the bulk weight or volume of a dosage form
- **Preservatives**-are substances that prevent or minimize the growth of bacteria or other microorganisms in the dosage form. Are agents in liquid and semisolid preparation to prevent microorganisms' growth.
- **Solvents**- are used to dissolve the drug substance.
- **Flavors and sweeteners**-are used to make the product more palatable. Are agents used to impart a pleasant flavor and often odor to pharmaceutical preparations.
- **Colorants**- are added to enhance appeal; are agents used to impart color to liquid and solid pharmaceutical preparations.
- **Antioxidant**- that are agents inhibit oxidation and thus are used to prevent the deterioration of preparations by the oxidation process.
- **Antiadherents or lubricants** -assist smooth tablet information.
- **Disintegrating agents**- promote tablet break up after administration and coatings to improve stability, control disintegration or enhance appearance.

- **Surfactants**- which adsorbed to surface or inter face to reduce surface or interfacial tension.
- **Emulsifying agents**- are agents required to stabilize emulsion
- **Thickenings agents**-are viscosity increasing agents used to reduce the rate of sedimentation of drug particle dispersed throughout a vehicle in which they are not suitable.

Types of dosage forms

There are generally three types of dosage forms including:

- **Solid dosage forms**: tablets, capsules, powders, granules, lozenges, pastilles
- **Semi-Solid dosage forms**: Ointments, Creams, Jellies, Pastes, Plasters, Glycerogelatin
- **Liquid dosage forms**: Solutions, Suspensions, Emulsions
- **Miscellaneous pharmaceutical dosage forms**: Aerosols, Sprays, suppositories, pessaries

2.5.1. Solid dosage forms

Tablets

Tablets are solid dosage forms containing the active ingredient with or without suitable diluents. Tablets are available in variety of sizes, shapes, color and thickness. They are formed in molds or produced by compression and are composed of one or more active ingredients and one or more inert substances. Most tablets are designed to be swallowed whole and dissolve in the gastrointestinal tract, but some are also made to be administered sublingually, buccally or vaginally.

Advantages of tablets

- 1- Compared to liquid dosage forms tablets possess more chemical and physical stability
- 2- Packaging in blister packs can also enhance the stability of tablets
- 3- They provide an accurately measured dose and low content variability of the unit dose
- 4- Low manufacturing cost
- 5- Easy to package and ship

6- Simple to identify (Coatings can be colored or stamped to aid tablet recognition)

7- Manufacturing processes and techniques can provide tablets special properties for example enteric coatings or sustained release formulations.

Disadvantages of tablets as a dosage form

1- Poor bioavailability of poorly soluble drugs or poorly absorbable drugs

2- Some drugs may cause local irritation and harm gastrointestinal mucosa

3- Some drugs resist compression into tablet

4- Difficulty in swallowing in some patients e.g. pediatrics and unconscious patients

5- they are not suitable in emergency cases; intravenous or intramuscular injections are more effective

Common types of tablets include:

- **Enteric-coated tablets:** are a type of tablets intended to release their contents in the small intestine bypassing the acidic stomach.
- **Sustained-release tablets:** are tablets designed to deliver their contents over time.
 - Some drugs are formulated to deliver their contents over 24 hours and only need to be taken once a day.
 - Sustained-release drugs should be swallowed whole; crushing may cause the contents to be released immediately.
- **Film coating and sugar coating tablets:** are tablets coated to mask their unpleasant taste and make them easier to swallow.
- **Chewable tablets:** are formulated for people who have difficulty swallowing pills.
 - Many children's medicines are available in a chewable dosage form.
- **Sublingual tablets and buccal tablets:** are tablets that are placed under the tongue (sublingual) or the cheek (buccal), dissolve in the mouth and absorbed to the blood stream directly.

- Drugs that are destroyed by stomach acids or need to get into the bloodstream rapidly (e.g., nitroglycerin) may be formulated for sublingual or buccal administration.
- **Tablets for Solution:**
 - Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablet: Potassium Permanganate Tablets for Solution
- **Effervescent Tablets:**
 - In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric
 - In the presence of water, these additives react liberating carbon dioxide which acts as a disintegrator and produces effervescence.
 - Except for small quantities of lubricants present, effervescent tablets are soluble.



Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials (excipients). They are classified according to the part they play in the finished tablet.

- ✓ those which help to impart satisfactory processing and compression characteristics to the formulation (diluent, binders, glidants and lubricants) and

- ✓ those which help to give additional desirable physical characteristics to the finished tablet (disintegrants, colors, and in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled- release tablets, polymers or waxes or other solubility-retarding materials)

Diluents

- ✓ is an inert substance added to increase the bulk in order to make the tablet a practical size for compression.
- ✓ Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar.

Binders

- ✓ Are agents used to impart cohesive qualities to the powdered material to insures the tablet remaining intact after compression, as well as improving the free- flowing qualities by the formulation of granules of desired hardness and size.
- ✓ Commonly used binders include: starch, gelatin and sugars such as sucrose, glucose, dextrose, and lactose.

Lubricants

- ✓ Lubricant have roles in tablet manufacturing
- ✓ Prevent adhesion of the tablet material to the surface of the dies and punches.
- ✓ Reduce inter particle friction.
- ✓ Facilitate the ejection of the tablets from the die cavity.
- ✓ May improve the rate of flow of the tablet granulation.
- ✓ Commonly used lubricants include: talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and (PEG).

Glidants

- ✓ promote the flow of the tablet granulation or powder materials by reducing friction among particles

Disintegrants

- ✓ Is a substance, or a mixture of substances, added to a tablet to facilitate its breakup or disintegration after administration.
- ✓ Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algin, gums and cross-linked polymers.

- ✓ The oldest and still the most popular disintegrants are corn and potato starch which have been well-dried and powdered.
- ✓ Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix.

Colors and dyes

- ✓ For attractiveness.
- ✓ Provide product identification.
- ✓ Produce a more elegant product.

Flavoring agents

- ✓ Are agents used to impart good odors for the formulation.
- ✓ Are usually limited to chewable tablets or tablets intended to dissolve in the mouth.

Artificial sweeteners: like flavors, are usually used only with chewable tablets or tablets dissolve in the mouth.

Adsorbents: (e.g., magnesium oxide, magnesium carbonate, bentonite, silicon dioxide) are substances capable of holding quantities of fluid in an apparently dry state.

Capsules

Are solid dosage forms which the solid or liquid drug is enclosed in a hard or soft soluble gelatin shell to mask its bad taste and odour. The gelatin shell dissolves in the stomach, releasing the drug. A capsule may contain powders, granules or crushed tablets with one or more active ingredients and one or more inert ingredients.



Advantage of encapsulation:

- Taste concealment (unpleasant taste)
- Elegance, smooth slippery, easily swallowed shell
- Nice presentation of the drug
- Portability, convenient
- Light weight
- Rapid drug release
- Can be used for the extemporaneous compounding of prescriptions.

1. Hard gelatin capsules



- ✓ The empty capsule shells are made from a mixture of gelatin, plasticizer, sugar and water (and may contain FD&C dyes and / or opacifying agent, preservative, enteric agent, flavour).

✓ **Gelatin**

- is obtained by partial hydrolysis of collagen obtained from bones, skin, connective tissue of animals.
- Non-toxic, used in food stuff.
- Readily soluble in biological fluid at body temperature
- Good film forming material
- Undergoes a reversible phase change at a little high temperature

✓ **Plasticizers:** Glycerol, sorbitol, propylene glycol.

- The ratio by weight of dry plasticizer to dry gelatin determine the hardness of the gelatin shell.

2. Soft Gelatin Capsules(SGC) or Soft elastic gelatin (SEG)



Pharmaceutical applications:

- 1-As an oral dosage form for human or veterinary use
- 2-As a suppository dosage form for rectal or vaginal use
- 3-As a specialty package in tube form, for single dose application of topical and ophthalmic preparations; rectal ointments; ear and nose drops.

Advantages of SGC as a dosage form:

- 1-A compression stage is not included.
- 2-The dose content uniformity is optimized, with reduction of the cost through the use of smaller averages.
- 3-Protection of sensitive drug from oxidation and hydrolysis.
- 4-The drug is dissolved or dispersed in vehicle which provides high surface area and good bioavailability.

Powders and Granules

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for external or internal use.

Granules, which are prepared agglomerates of powder material, may be used perse for the medicinal value of their content or they may be used for pharmaceutical purpose, as in making tablets.

Medicated Powders

Some medicated powders are intended to be used internally; others, externally. Most powders for internal use are taken orally after mixing with water. Some powders are intended to be inhaled for local and systemic effects.

Medicated Powders may be provided to the patient in bulk and divided. Some powders are packaged by manufacturers, where as others are prepared and packaged by the pharmacist.

Bulk powders

- ✓ The substance prescribed in this form are bulky powder. Such as light and heavy magnesium carbonate, magnesium trisilicate, etc.

Among the bulk powders available in prepackaged amount are:

- a. Antacids (e.g. sodium bicarbonates) and laxatives (e.g. psyllium) which the patients take by mixing with water or other beverages.
- b. Douche powders (e.g. massengil powder), dissolved in warm water by the patient for vaginal use.

Divided Powders

- ✓ This form of powder may contain one or more drugs together, it may be divided in to individual dosing units based on the amount to be taken or used at a single time. Divided powders are prepared by geometric dilution techniques.



Lozenges

- It is a solid preparation consisting of sugar and gum, the latter giving strength and cohesiveness to the lozenge and facilitating slow release of the medicament.
- It is used to medicate the mouth and throat for the slow administration of indigestion or cough remedies.



Pastilles

They are solid medicated preparations designed to dissolve slowly in the mouth. They are softer than lozenges and their bases are either glycerol and gelatin, or acacia and sugar.



2.5.2. Semi-solid dosage forms

These dosage forms are too thick to be considered a liquid dosage form and not solid enough to be considered a solid dosage form.

Semi-solid dosage forms may be:

- ✓ **Medicated:** - are semi-solid dosage forms that contain a therapeutic agent and they are mostly used to treat skin conditions
- ✓ **Un-medicated:** - are those semi-solid preparations which are used for their physical effect, that is, for their ability to act as skin protectant, lubricant, emollient or drying agents.
 - Topical applications can be designed for either local effects or systemic absorption.
 - A local dermatological product is designed to deliver drug into the skin in treating dermal disorders, with the skin as a target organ.

Advantages of semisolid dosage forms

- ✓ Have site specific action with no or little systemic side effect
- ✓ Convenient; unconscious patient or difficulty in oral administration
- ✓ Prolong residence after application compared to solid and liquid dosage form
- ✓ Chemically stable and easy to handle compared to liquid dosage form

Disadvantages of semisolid dosage forms

- ✓ Staining and cosmetically less appealing
- ✓ difficult to handle compared to tablets
- ✓ Quantity of dose is not accurate

There are four types of semisolid dosage forms: Ointments, creams, gels, pastes

Ointments

- Are semi-solid, greasy preparations containing the medicinal agent intended for use for application on skin or mucous membranes.
- They are soft hydrocarbon based semisolid preparations, composed of fluid hydrocarbon meshed in a matrix of higher melting solid hydrocarbon, e.g. petrolatum.
- Since they are of greasy nature so they stain cloths, are generally poor solvent for most drugs, and usually decrease the drug delivery capabilities of the system.
- Ointment can be medicated or non-medicated, the later type commonly being referred to as ***ointment bases***
- **Ointment bases** are used as such for their emollient or lubricating effect or used as vehicle for the preparation of medicated ointment.

Creams

- Creams are emulsions for external use as protective or emollients to soften and sooth
- **creams** are defined as semisolid emulsions of either oil in water or water in oil type.
 - semisolid emulsions usually medicated, intended for external application.
 - Creams of W/O type include cold cream and emollient cream.
 - Creams of O/W type include hand cream, shaving cream and foundation cream.
- Creams are formulated to provide preparation that are essentially miscible with skin secretion. They are intended to be applied to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes especially when occlusive effect is not necessary.
- They are viscous semisolid emulsion system with opaque appearance compared with the translucent ointments.
- Properly designed O/W creams are elegant drug delivery system, pleasing in both appearance and feel after application.
 - ✓ O/W creams are non-greasy and are rinsable.
 - ✓ They are good for most topical purposes.

Cosmetic creams

- ✓ All purpose cream, baby cream, barrier cream, bleaching cream, cleansing cream cold cream, hair cream, hand cream, vanishing cream.

Medicated creams

- ✓ Creams are reserved for external preparation.
- ✓ A cream may be water in oil or oil in water depending on the emulsifying agent used.
- ✓ They are soft, easy to apply, cooling to skin, easily water-removable.
- ✓ W/o cream: oily creams
 - Contains: emulsifying agents of natural origins (bees wax, wool alcohols, wool fat)
 - properties: Creamy, white or translucent and stiff
- ✓ O/w creams: aqueous creams
 - Contains: synthetic waxes e.g., cetomacrogols & macrogols
 - Properties: Causes rapid absorption & penetration, Thin, white & smooth consistency.

Gels

- Gels are transparent or translucent non-greasy semisolid preparations.
- Some are as transparent as water itself, an aesthetically pleasing state, other are turbid, as the polymer is present in colloidal aggregates that disperse light.
- They are used for medication or lubrication.
- Topical: Applied to any external body surface
 - **Labelled for** “External Use Only”
- **Transdermal designed** to deliver drug through skin (percutaneous absorption) – general circulation

Pastes

- ✓ Pastes are basically ointments into which a high percentage of insoluble solid has been added.
- ✓ The extraordinary amount of particulate matter stiffens the system.
- ✓ Pastes are less penetrating than ointment.

- ✓ Paste make particularly good protective barrier when placed on the skin for, in addition to forming an unbroken film, the solid they contain can absorb and thereby neutralize certain noxious chemicals before they ever reach the skin.
- ✓ Like ointments, paste forms an unbroken relatively water impermeable film.
- ✓ Unlike ointments, the film is opaque and therefore, an effective sun block accordingly.
- ✓ Dermatologic pastes are ointment like preparations employed in practice of dermatology
- ✓ Usually stiffer, less greasy and more absorptive than ointments such as starch, ZnO, CaCO₃, and talc in the base.

2.5.3. Liquid dosage forms

Liquid dosage forms contain one or more active ingredients in a liquid vehicle such as a solution, suspension or emulsion. They are easier to swallow, particularly for pediatric patients.

Solutions

Are liquid preparations prepared by dissolving active medicinal substance in a solvent. It is an evenly distributed (homogenous) mixture of one or more dissolved medications (solutes) in a liquid vehicle (solvent). It can be for internal or external use. Solutions can be classified by vehicle as an aqueous solution (water based), an alcoholic solution (alcohol-based), or a hydroalcoholic solution (water and alcohol-based).

Advantages of solutions as an oral dosage form

- ✓ Liquids are easier to swallow than solids and are therefore particularly acceptable for pediatric and geriatric use.
- ✓ Absorption is not delayed while solution takes place in the gut (in contrast to solid dosage forms and oral suspensions).
- ✓ A solution is a homogenous system and therefore, the drug will be uniformly distributed throughout the preparation. In suspension or emulsion formulations, dose variation can occur as a result of phase separation on storage.
- ✓ provide a safe means of administering substances like potassium iodide and bromide that can irritate and damage the gastric mucosa if taken dry e.g. As powder or tablet.

Disadvantages of solution as an oral dosage form

- ✓ Liquids are bulky and therefore inconvenient to handle, transport and store

- ✓ If the container breaks, the whole of the product is immediately and irreversibly lost
- ✓ The stability of ingredients in aqueous solution is often poorer than if formulated as tablet or capsule, particularly if they are susceptible to hydrolysis.
- ✓ Solutions often provide suitable media for the growth of microorganisms and may therefore require the incorporation of preservative.
- ✓ Difficulty in masking the unpleasant taste of the drug.

Solutions can be classified by their contents as:

Aromatic water

- Aromatic waters are aqueous solutions, usually saturated, of volatile oils or other volatile substances that are characterized by very low water solubilities.
 - e.g. chloroform
- Aromatic waters are used externally as perfumes (e.g. Rose Water), and internally as flavoring agents (e.g. Peppermint Water, Cinnamon Water and Orange Flower Water) and/or as medicaments (e.g. Peppermint Water has been used as a carminative and Chloroform Water was used in expectorant preparations).

Elixirs

- are clear, sweet solution that contains dissolved medication in a base of water and ethanol (hydroalcoholic) intended for oral use.
- They can contain either alcohol soluble or water-soluble drugs.
- Non-medicated elixirs are employed as vehicles and medicated elixirs are used for the therapeutic effect of the medicinal substances they contain.
- They usually contain potent drugs such as antibiotics antihistamines and sedatives and are formulated to be palatable and, generally, very stable.
- Compared with syrups, elixirs are usually less sweet and less viscous because they contain a lower proportion of sugar and consequently are less effective than syrups in masking taste of medicinal substance.
- Although many elixirs are sweetened with sucrose or with sucrose syrup, some use sorbitol, glycerin, and/or artificial sweeteners.
- They contain between 5% and 40% alcohol.

- Elixirs having a high alcoholic content usually use an artificial sweetener, such as saccharin, which is required only in small amounts, rather than sucrose which is only slightly soluble in alcohol and required greater quantities for equivalent sweetness.
- All elixirs contain flavorings to increase their palatability, and most elixirs have coloring agents to enhance their appearance self- preserving and do not require the addition of an anti microbial agent.
 - One advantage of elixirs over their counterpart drugs in solid dosage forms is the flexibility and ease of dosage administration to patients who have difficulty swallowing solid forms.
 - A disadvantage of elixirs for children and for adults who choose to avoid alcohol is their alcoholic content.

Linctuses

- are viscous oral liquids that may contain one or more active ingredients in solution.
- The vehicle usually contains large amounts of sucrose, other sugars or a suitable polyhydric alcohol or alcohols.
- are intended for use in the treatment or relief of cough, being sipped and swallowed slowly without the addition of water.
- They contain medicaments which have demulcent sedative or expectorant action.

Syrup

- Is a sugar-based (e.g. Sucrose) solution that may be medicated or non-medicated.
- Medicated syrups are employed in therapeutics for the value of the medicinal agent present in the syrup.
- Syrups provide a pleasant means of administering a liquid form of a disagreeable- tasting drug
- Syrups containing flavoring agents but not medicinal substances are called non-medicated or flavored vehicles (syrups)
- Flavored syrups are a convenient form of masking disagreeable tastes
 - serve as pleasant tasting vehicles for medicinal substances to be added in the extemporaneous compounding of prescriptions

Extract

- Is a powder or liquid derived from animal or plant sources in which all or most of the solvent has been evaporated.

Tincture

- Is an alcoholic or hydro alcoholic solution of non-volatile substances.

Spirits

- Are alcoholic or hydroalcoholic solutions of volatile substances (usually volatile oils)
- Some spirits are used internally for their medicinal value, a few medicinally by inhalation. But a large number are used as flavoring agents.

Irrigating solution

- Is a solution that is used for cleansing an area of the body

Solutions can also be classified by their method of administration as Oral, external and parenteral solutions.

Oral solutions

- Oral solutions are clear liquid preparations for oral use containing one or more active ingredients dissolved in a suitable vehicle

For external use solutions

Drops

- ✓ are aqueous preparations intended for topical administration to the nose, throat, eye or ear.
- ✓ Eye drops should be clear and sterile aqueous solutions, adjusted to a suitable pH and osmotic pressure.

Gargles:

- are aqueous solution used to treat disease of the pharynx or nasopharynx and as deodorant or antiseptic.
- They are brought in to intimate contact with the mucous membrane of the throat and are allowed to remain in contact with it for few seconds, before they are thrown out of the mouth.
- They are used to relief soreness in mild throat infections

- They usually contain a bactericide e.g. Phenol or thymol, and are dispensed in concentrated forms with direction for dilutions with warm water before use.
- Potassium chlorate is also included in gargles for its weak stringent effect to tone up a relaxed throat. It also stimulates secretion of saliva which relieves dryness.

E.g. Phenol gargles

Enemas

- ✓ are aqueous or oily solutions, suspensions or emulsions of medicaments intended for rectal administration for the therapeutic, cleansing or diagnostic purposes.
- ✓ **The cleansing enema**
 - are used to evacuate feces in case of constipation or before operation (Evacuation enemas)
 - Cleansing enemas act in one of two ways
 - One, by stimulating peristalsis because either their volume is large (0.5 – 1 liter) or they cause osmotic retention of water in the bowel. These types are of smaller volume e.g. Sodium phosphates enema (100ml) and magnesium sulphate enema.
 - The other is, by lubricating impacted feces e.g. Olive and arachis oil enemas (100 – 550ml)
- ✓ **The therapeutic enema**
 - are used to influence the general system by absorption or retention enema
 - therapeutic enemas may be used as sedatives, antihelmentics anti-inflammatory agents, nutrients etc.
- ✓ **Diagnostic enema:**
 - Enemas used for diagnostic purposes contain radio opaque substances for x-ray examination of the lower bowel e.g. Barium sulphate enema

Collodions

- ✓ Collodions are liquid preparations composed of pyroxyline (a nitro cellulose i.e. soluble gun cotton, collodion cotton), dissolved in a solvent mixture usually composed of alcohol and ether with or without added medicinal substances.
- ✓ Collodions, when applied to the skin, the solvent rapidly evaporates, leaving a filmy residue of pyroxyline. This provides an occlusive protective coating to the skin and when

the collodion is medicated, it leaves a thin layer of that medication firmly placed against the skin.

- ✓ Naturally, collodions must be applied to dry tissues to adhere to the skins surface
- ✓ The products must be clearly labeled “for external only” or with words of similar effect.

Liniments

- ✓ Liniments are alcoholic or oleaginous solutions or emulsions of various medicinal substances intended to be rubbed on the skin.
- ✓ Liniments with an alcoholic or hydro alcoholic vehicle are useful when rubefacient, counter irritant or penetrating action is desired.
- ✓ Oleaginous liniments are employed primarily when massage is desired. By their nature, oleaginous liniments are less irritating to the skin than alcoholic liniments.
- ✓ Liniments are not applied to skin areas that are broken or bruised because excessive irritation might result.

A parenteral solution

- Is a sterile solution that is administered by a needle or catheter via injection or infusion
- Injectable dosage forms are marketed in ampules, vials, pre-filled syringes, and pre-filled infusion bags.

Suspension

- Liquid preparations for oral use containing one or more active ingredients suspended in a suitable vehicle.
- may show a sediment which is readily dispersed on shaking to give a uniform suspension which remains sufficiently stable to enable the correct dose to be delivered
- Every suspension should have a label “shake well before use”
- Flavored syrups are a convenient form of masking disagreeable tastes
- Some suspensions are available in ready to use the, that is already distributed through a liquid vehicle with or with out stabilizers and other additives
- Other preparations are available as dry powders intended for suspension in liquid vehicles. This type of product generally is a powder mixture containing the drug and suitable

suspending and dispensing agents to be diluted and agitated with a specified quantity of vehicle, generally purified water.

- Drugs that are unstable if maintained for extended period in the presence of an aqueous vehicle (for example, many antibiotics drugs) are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing.
- Suspensions offer an alternative oral dosage form for patients who cannot swallow tablet or capsule such as pediatric and geriatric patients.
- Suspensions are often used to deliver poorly water-soluble drugs that cannot be formulated as a solution

Desirable Features of Pharmaceutical suspensions

There are many considerations in the development and preparation of pharmaceutically elegant suspensions. In addition to therapeutic efficacy, chemical stability of the components of the formulation, permanency of the preparation and esthetic appeal of the preparation desirable qualities in all pharmaceutical preparations a few other features apply more specifically to the pharmaceutical suspension.

1. After shaking the medicament should stay in suspension long enough for removal of the correct dose from oral products and corrects proportion of active ingredients from external applications. To achieve this aim, it is often necessary to use a suspending agent.
2. A properly prepared pharmaceutical suspension should settle slowly and should be readily re-dispersed upon gentle shaking of the container.
3. The suspension should pour readily and evenly from its container
4. The particle size of suspensoid should remain fairly constant throughout long period of undisturbed standing
5. It is comparatively free from large particles which spoil appearance, give a gritty taste to oral preparations and make external products irritating to sensitive tissues.

Major Applications: Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, instilled intranasally, inhaled into the lungs, applied to the skin or topical preparations, or used for ophthalmic purposes in the eye.

The physical properties of suspensions and their design depend up on the nature of the dispersed phase, the dispersion medium and the pharmaceutical adjuncts/ additives.

2.2.Comparison between flocculated and non-flocculated suspensions

Flocculated suspension	Non-flocculated suspension
-Particles form loose aggregates and form a network like structure	- Particles exist as separate entities
-The rate of sedimentation is high	- The rate of sedimentation is slow
-Sediment is rapidly formed	- Sediment is slowly formed
-Sediment is loosely packed and does not form a hard cake	- Sediment is very closely packed and a hard cake is formed
-Sediment is easy to redisperse	- Sediment is difficult to redisperse
-Supernatant liquid is clear	- Supernatant liquid is not clear

Emulsions

An emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout the vehicle (dispersion medium, external phase or continuous phase) in which it is immiscible with the help of a third agent called emulgent (emulsifying agent).

Normally, two immiscible liquids cannot be dispersed for a long period. So, an emulsifying agent is added to the system. It forms around the globules in order to scatter them indefinitely in the continuous phase, so that a stable emulsion is formed.

Advantage of Emulsions

- Medicines having unpleasant taste and odor can be made more palatable for oral administration in the form of an emulsion. E.g. Castor oil, Cod-liver oil etc
- Emulsion provides protection against drugs which are prone to oxidation or hydrolysis
- Various external preparations such as creams, lotion and foam aerosols are formulated in emulsion.
- The sterile stable intravenous emulsions containing fats carbohydrates and vitamins can be administered to the patients who are unable to take them orally.

Types of Emulsions:

- ✓ The emulsions are of two types

- Oil in water type (O/W)
- Water in oil type (W/O)
- ✓ In oil in water type emulsion, the oil is in dispersed phase where as water is in the continuous phase.
 - In these emulsion, gum acacia, tragacanth, methyl cellulose, saponins synthetic substances and soaps formed from monovalent bases like Na^+ , K^+ and NH_4^+ are used as emulsifying agents
- ✓ Pharmaceutical emulsions may be prepared as liquids or semisolids. Based on the constituents and the intended application, liquid emulsions may be employed orally or topically.
- In water-in- oil type emulsion, the water is in the dispersed phase where as oil is the continuous phase.
 - The wool fat, resins, beeswax, and soaps from divalent bases like Ca^{++} , Mg^{++} and Zn^{++} are used as an emulsifying agent.
- For orally administered emulsions, the O/W type permits palatable administration of an otherwise distasteful oil by dispersing it in a sweetened, flavored aqueous vehicle.
- Emulsions to be applied to the skin may be O/W or W/O, depending on such factors as the
 - **Nature of therapeutic agents:** - Medicinal agents that irritate the skin generally are less irritating in the internal phase of an emulsified topical preparation than in the external phase, from which direct contact with the skin is more prevalent.
 - **The desirability for an emollient or tissue softening effect and condition of the skin:**
 - On the unbroken skin, a W/O emulsion can usually be applied more evenly, because the skin is covered with a thin film of sebum, and this surface is more readily wetted by oil than water.
 - A W/O emulsion is also more softening to the skin, because it resists drying and removal by contact with water.
 - On the other hand, if it is desirable to have a preparation that is easily removed from the skin with water, an O/W emulsion is preferred.

2.5.4. Miscellaneous dosage forms

Suppositories

- Are small solid medicated mass, usually cone shaped, that is inserted either into the rectum (rectal suppository), vagina (vaginal suppository or pessaries) where it melts at body temperature.
- The suppository base is an inactive ingredient, which melts or dissolves in the body cavity, releasing the medication.
- Suppositories are often used in children and in adults who are unable to take oral medications.
- Rectal suppositories are conical or bullet shaped, vaginal suppositories spherical, and urethral suppositories pencil shaped.



Why do we need suppositories?

1. To provide local effect on the rectum.
Example: - Antinflammatory agent for treatment of hemorage.
2. To provide systemic effect.
3. To promote evacuation
4. For patients who are unconscious, mentally disturbed, unable to tolerate oral medication b/s of vomiting and GIT problem

5. For gastric irritant drug
6. To treat infants
7. To avoid gastric environment and bypass portal circulation
8. Good absorption of rectal cavity than oral

Disadvantage of Suppositories

1. Psychological barrier/pt inconvenience
2. Inflammation of rectum and anal area

The properties of an ideal suppository base are: -

- Melts at body temperature or dissolves in body fluids.
- Non-toxic and non-irritant.
- Compatible with any medicament.
- Releases any medicament readily
- Easily moulded and removed from the mould
- Stable to heating above the melting point
- Resistant to handling
- Stable on storage

Preparation of suppositories: - suppositories are prepared by **suppositories Molds** and **contains drug substances and Suppositories bases.**

- ✓ Base + drug substance



- **There are two main classes of suppository base**
 - **Fatty bases designed to melt at body temperature**
 - **Water-soluble or water-miscible bases designed to dissolve or disperse within the body**
 - Example of base: - theobroma oil

Pessaries

- ✓ Pessaries are a formulations intended through vaginal route
- ✓ They are intended to provide local action in case of vaginitis, Leucorrhoea (unpleasant discharge from Vaginal)
- ✓ Vaginal dosage forms may be successfully employed to provide a local effect for the treatment of infection (fungal and bacterial) and for the treatment of hormone deficiency (topical hormone replacement therapy for the treatment of vaginal atrophy).
- ✓ Vaginal dosage forms may be employed to provide systemic drug absorption of certain therapeutic agents. Examples of these applications include:
 - steroid hormones (e.g. oestradiol acetate) for the treatment of the systemic symptoms of the menopause and for long-term contraception
 - prostaglandins (for cervical ripening).

Aerosols

Aerosols are colloidal system very fine drug particles or droplets dispersed(dissolved). **Example:**

- Perfumes, Deoderant, Insecticides, drugs like- Salbutamol, hydrocortisone

Advantage of Aerosols

- ✓ Less risk of contamination
- ✓ Tamper proof- difficult to alter the content of an Aerosol.
- ✓ They are hermetically sealed. Especially for volatile substance, liquids, oxidizable.
- ✓ Thin layer application to skin with out touching.
- ✓ Example: - inflamed skin treatment: Accurate of dosage is more

Activity: Dear trainees, try to identify, compare and contrast various dosage forms of sample drugs you will be shown by your facilitator.

2.6. Routes of drug administration

Routes of drug administration are the path by which a drug is brought into contact with the body.

The way in which the body absorbs and distributes drugs varies with the route of administration.

Drugs may be given either for their local action at their site of administration or for systemic effect.

When a drug has a systemic effect, the effect is on entire body.

There are generally two major categories of routes of drug administration:

- Enteral
- Parenteral
- Others

Enteral route

The enteral routes of administration are those in which the drug is placed directly in the alimentary tract, i.e., from the mouth to the rectum. There are four enteral routes of administration: Oral, sublingual, buccal and rectal routes.

Oral route

Refers to the administration of drugs through the mouth for systemic effect or for local purpose. It is usually abbreviated as PO (Latin per os, meaning through the mouth). Common oral formulations include tablets, capsules, solutions, emulsions, syrups, suspensions, and elixirs.

Advantages

- Oral dosage forms are easy to carry, use and administer
- Often painless, need no assistance for administration
- No risk of infection and relatively safe

Disadvantages

- Action slower and thus not suitable for emergencies
- Unpalatable drugs difficult to administer
- Not suitable for uncooperative /unconscious/ vomiting patients
- Absorption of many drugs is affected by the presence food in the stomach
 - E.g. Absorption is slower with food (milk and milk products) for tetracyclines
- Certain drugs cannot be taken orally because they are degraded by stomach acid and intestinal enzymes e.g. Penicillin G

NB. For the instructor: let the students visit nearby pharmacy to identify some drugs given by this route

Sublingual and buccal

In sublingual administration, a drug product is placed under the tongue. In buccal administration, the drug is placed between the cheek and the gum. Examples of drugs administered by this route: vasodilators like nitroglycerin.

Advantage

- Prevent the destruction of the drug by low pH in the stomach
- Rapid absorption and rapid onset of action

Disadvantages

- Inconvenient
- Small doses only can be accommodated easily
- Unpleasant taste of some drugs
- Irritation of oral mucosa & excessive salivation

NB. For the instructor: let the students visit nearby pharmacy to identify some drugs given by this route.

Rectal

Certain unpleasant drugs can be put into the rectum as suppositories or enema for systemic effect.

This route is preferred route when:

- drugs are administered to relieve constipation or hemorrhoids
- The patient is unconscious and uncooperative patients (e.g., children)
- Nausea and vomiting make patient unable to take oral drugs

Disadvantages

- Patients may be embarrassed and dislike this way.
- Irritation of mucosa & inflammation may occur with repeated use
- Not suitable for Emergency (slow onset of action)

Parenteral route: Par = beyond and enteral = intestine

It refers to any sites of administration that are outside of or beside the alimentary tract.

Drugs are directly introduced into tissue fluids or blood without having to cross the intestinal mucosa. Several parenteral routes require a needle and some type of propelling device (syringe, pump) to administer a drug. To avoid introducing contaminants that are harmful if injected into a patient, parenterally administered drugs are prepared using aseptic technique in a sterile environment.

The following are examples of parenteral drugs:

- Intravenous (IV) solutions are injected or infused directly into a vein and go immediately into the bloodstream.
- Intramuscular (IM) solutions and suspensions are injected deep into a skeletal muscle.

- Subcutaneous (subcut) solutions and suspensions are injected just beneath the skin.
- Intraarticular solutions are injected directly into a joint.

Advantages

- Action faster (hence valuable in emergencies)
- Employed in unconscious/uncooperative/vomiting patients
- No interference of food or digestive juice and first pass effect is bypassed to a certain extent.

Disadvantages

- Cost: many parenterals are more expensive than enteral route preparations
- Require skilled personnel to administer them
- Once administered, it is difficult to remove the dose in case of toxicity

The major parenteral routes include: Intravenous (IV), Intramuscular (IM) and subcutaneous (SC).

An intravenous injection:

- It is a liquid administered directly into the bloodstream via a vein.
- It is advantageous when a rapid onset of action is needed.

Intramuscular injection

- It is the injection of a substance directly into a muscle
- are often given in the deltoid, vastus lateralis, ventrogluteal and dorsogluteal muscles

Subcutaneous injection:

- Subcutaneous injections are given by injecting a fluid into the subcutis, the layer of skin directly below the dermis and epidermis.
- Subcutaneous injections are highly effective in administering vaccines and such medications as insulin.

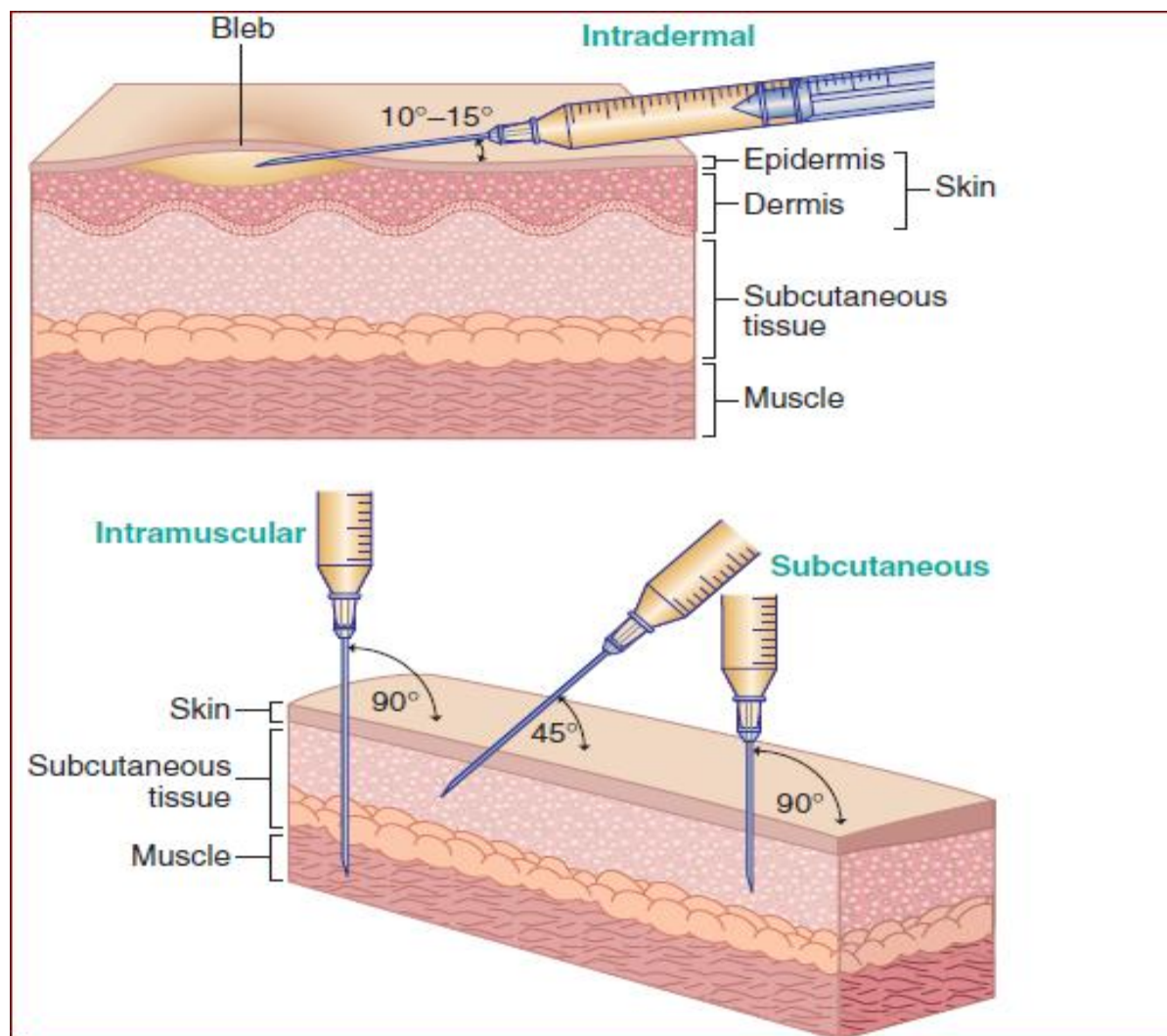


Figure 2.1. Different parenteral route of drug administration

Other routes of drug administration

Drugs can be administered by a number of routes in addition to those already discussed.

- Drugs can be applied topically for local therapy of the skin, eyes, ears, nose, mouth, and vagina.
 - topical dosage forms include: ointments, creams, and suppositories, Solutions, suspensions, and emulsions
- Some drugs are **inhaled** to elicit local effects in the lung, especially in the treatment of asthma.

- Microfine powders, solutions, and gaseous drugs are inhaled into the lungs using a metered-dose aerosol inhaler (**Figure 2.2**) or a nebulizer.
- A nebulizer is a device that turns solutions into vapors that can be inhaled.
- Other **inhalational agents** (e.g., volatile anesthetics, oxygen) are used for their systemic effects.
- Rectal suppositories may be employed for local effects or for effects throughout the body.
- Vaginal suppositories may be employed to treat local disorders.



Figure 2.2. Inhalational route of drug administration

Group activity: Be in group and discuss advantage and disadvantages of different routes of drug administration with regard to dosage form of drug available for administration, costs and easiness of administration.

2.7. Pharmacokinetics

What is pharmacokinetics?

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs from the body. Simply put, it is the study of “**what the body does to drugs**”.

There are four basic pharmacokinetic processes: Absorption, Distribution, Metabolism, and Excretion (ADME).

All the pharmacokinetic processes involve passage of drug through cell membranes. Cell membranes are bilayer of amphipathic lipids, with their hydrocarbon chains oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outwards. Membrane proteins embedded in the bilayer serve as structural anchors, receptors, ion channels, or transporters to transduce electrical or chemical signaling pathways and provide selective targets for drug actions.

Passage of drugs through cell membranes follows one or a combination of the following major mechanisms.

- Passive diffusion
- Pore transport (filtration)
- Carrier mediated transport
- Endocytosis

Most drug absorption occurs through passive diffusion. Lipid soluble drugs are more readily absorbed than non-lipid soluble drugs.

A. Absorption

- Absorption is the process by which the drug enters in to the systemic circulation from the site of administration through biological barrier.
- In case of intravenous or intra-arterial administration the drug by passes absorption processes and it enters into the circulation directly.
- By contrast, drugs administered extravascularly need to be carried through various barriers in order to be able to reach the blood circulation and then their site of action.
- The most widely employed extravascular route of administration is the oral route.

- In this case, the drug first reaches the stomach where it usually disintegrates and dissolves in the gastric lumen.
- It is then evacuated in the small intestine.
 - Because of its permeability, large surface area and high blood flow, the small intestine is the primary site for absorption.
- Therefore, gastric emptying is an important factor influencing the rate of drug absorption.
 - Foods, especially fat, can slow gastric emptying.
- Absorption can be limited by the short transit period of the drug through the small intestine (2-4 hours).
- Colon is usually a poor site of absorption due to its low permeability and relatively low surface area.
 - Nevertheless, some drugs are absorbed at this site because of the long period of transit (24-48 hours).

Bioavailability

Bioavailability is defined as: fraction of a dose of drug that is absorbed from its site of administration and reaches, in an unchanged form, the systemic circulation.

- Bioavailability of a drug administered intravenously is by definition 100%.
- Bioavailability is less or equal to 100% for any other route of administration

B. Distribution

It is the process by which absorbed drug or drug directly introduced into the circulation is carried to various sites within the body. It is a necessary step for the active molecules to reach their pharmacological target. Rate and/or extent of drug distribution is affected by:

- Properties of drugs
 - Lipid soluble drugs are well distributed
 - Degree of plasma protein binding-unbound drugs are easily distributed
- Physiological factors
 - Rate of blood flow increases drug distribution
- Presence of barriers

- Anatomical structures that selectively limit drug access are the blood-brain barrier, blood-placenta barrier, and blood-testicular barrier.

C. Metabolism

Drug metabolism, also called biotransformation, is a process by which drugs are chemically changed in the body as a result of their interaction with cells or tissues. The purpose of metabolism is to facilitate excretion of drugs by rendering them more polar (water soluble) or by conjugating it with highly polar molecules.

Drug metabolism usually occurs in the liver, but occasionally can take place in the gastrointestinal tract, lungs, kidneys, skin or plasma. Patients with liver disease may require lower dosages of a drug detoxified by the liver, or a drug that does not undergo a biotransformation by the liver.

Biotransformation is enzymatic in nature. The cytochrome P450 enzyme system is the major in terms of catalytic versatility and the number of drugs it metabolizes to inactive or active metabolites. Some times pharmacologically inactive drugs may be given to be converted to active drug in the body. Such drugs are referred to as prodrugs. Example, levodopa which is inactive (prodrug) is converted to dopamine which active after metabolism in the body.

2 (two) Phases of drug metabolism:

Phase I metabolism: it consists of oxidation, reduction and hydrolysis reactions

- Parent drug is altered by introducing or exposing a functional group (-OH, -NH₂, -SH)

Phase II metabolism [conjugation reaction]

Conjugating compounds include: Glucoronide [CAF, Morphine, sulphonamide, ASA], Acetyl [INH, hydralazine], Sulphate [steroids], Methyl [catecholamine], Glycine [nicotinic acid, ASA]

Conjugates are highly polar, and generally biologically inactive.

D. Excretion

Drug excretion is the elimination (passage out) of a systemically absorbed drug from the body in the form of metabolites or unchanged drug.

- The kidneys are the main organ of excretion of drugs and their metabolites.

- Patients with kidney disease may, thus, need a dosage reduction and careful monitoring of kidney function.
- Children have immature kidney function and may require dosage reduction and kidney function tests.
- Similarly, older adults have diminished kidney function and require careful monitoring and lower dosages.
- Other drugs are eliminated by sweat, breast milk, breath, or by the gastrointestinal tract in the feces.

Generally, only hydrophilic molecules are excreted effectively. Drugs may be excreted as unchanged parent molecules if they are sufficiently hydrophilic. Lipophilic drugs must be bio transformed to hydrophilic drug metabolites to be excreted.

Half-Life

Half-life refers to the time required for the body to eliminate 50% of the drug. Knowledge of the half-life of a drug is important in planning the frequency of dosing. For example, drugs with a short half-life (2–4 hours) need to be administered frequently, whereas a drug with a long half-life (21–24 hours) requires less frequent dosing. It takes five to six half-lives to eliminate approximately 98% of a drug from the body.

Plasma drug concentration and elimination

There is a direct correlation between therapeutic and toxic responses and the amount of drug present in plasma.

Minimum Effective Concentration: - The plasma drug level below which therapeutic effects will not occur

Toxic Concentration: - The plasma level at which toxic effects begin is termed the *toxic concentration*. Doses must be kept small enough so that the toxic concentration is not reached

2.8. Pharmacodynamics

What is pharmacodynamics?

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and their mechanisms of action. It deals “**what the drug does to the body**”.

How do drugs work?

Most drugs interact with **receptors** to produce their characteristic effects. **Receptors** are functional macromolecular components of the organism with which the drug interacts to elicit a cellular response, i.e., a change in cell function.

The lock and key model of signal-receptor interaction



Like a lock and key, only certain drugs are able to interact with certain receptors.

A ligand such as a hormone or neurotransmitter (the ‘key’) bind to specific receptors (the ‘lock’) and results in the cell’s response. Many drugs work by mimicking a naturally occurring hormone or transmitter. If the drug causes the receptor to respond in the same way as the naturally occurring endogenous regulatory molecules (hormones or neurotransmitters), then the drug is referred to as an **agonist**. If the drug binds to the receptor but doesn’t produce a response, the drug is referred to as an **antagonist**. Because the drug prevents the receptor from binding to the normal hormone or neurotransmitter, it has an inhibitory effect on the naturally occurring substance. If you conceptualize drug-receptor interactions as a “lock and key” model, agonists are keys that fit into a lock (receptor) and open (activate) them, whereas antagonists fit into the lock and jam the mechanism.

Two fundamental properties of agonists are affinity and efficacy.

- **Affinity** can be defined as the ability with which a drug binds to its receptor.
- **Efficacy** is ability of a drug to produce its biological effect.

Affinity gets the drug bound to the receptor, and efficacy determines what happens once the drug is bound.

Different drugs that bind to the same receptor and produce the same type of response will typically differ from each other in terms of their **potency) and/or efficacy**.

- The term potency is the amount of drug required to produce an effect of given intensity.
 - The drug which can produce an effect at lower drug concentrations is “**more potent**”.
- **Efficacy** is the ability of a drug to produce a response

Efficacy is more important than potency when determining usefulness of a drug unless the dose that is required to produce the therapeutic effect is so large that it is impractical to administer.

Activity: Cimetidine or Ranitidine can be used for treatment of gastric ulcer. Cimetidine is effective at a dose of 800mg/per day. Ranitidine is effective at a dose of 300mg/day. Which drug do you think is more potent and why?

Although the effects of most drugs result from drug-receptor interactions, some drugs do not act through receptors.

- Rather, they act through simple physical or chemical interactions with other small molecules.

Common examples include **antacids** and **saline laxatives**

- Antacids reduce gastric acidity by direct chemical interaction with stomach acid.
- Magnesium sulfate, a powerful laxative, acts by retaining water in the intestinal lumen through an osmotic effect.

And some drugs have no clearly known mechanisms of action e.g. general anesthetics.

Therapeutic Index (TI)

- All drugs can produce toxic effects that can lead to death
- When the lethal dose of a drug is close to the effective dose, the drug is not very safe.
- The safest drugs have a wide margin between the lethal dose and the effective dose.
- The therapeutic index (TI) is the ratio of the effective dose to the lethal dose ($TI=LD50/ED50$);
 - ED50 represents the effective dose for 50% of a population, and
 - LD50 is the lethal dose for 50% of a population.
- It represents an estimate of the safety of a drug, since a very safe drug might be expected to have a very large toxic dose and a small effective dose
- **The larger the TI, the safer the drug is.**
- Examples of drugs with narrow therapeutic index are: aminoglycosides, digoxin, and phenytoin. Wide therapeutic index drugs include penicillins.

2.9. Adverse Drug Reactions (ADR)

Drugs produce desired effects (therapeutic effects) and undesired effects. Undesired effects are called adverse reactions. Patients may experience one or more adverse reactions (side effects) when they are given a drug. E.g. Diarrhea with ampicillin and potassium loss with diuretics. ADRs may be mild, severe, or life threatening. ADR may occur after the first dose, after several doses, or even after many doses. Adverse effects may cause minor discomfort such as a rash, or they may be life threatening (e.g., coma and death).

Some common forms of ADR

Common adverse effects that occur in the central nervous system are drowsiness, dizziness, stimulation, or confusion. Life-threatening central nervous system effects include respiratory depression, coma, and death.

Hepatotoxicity

Hepatotoxicity is a toxic adverse reaction that occurs in the liver. Some common drugs that can produce hepatotoxicity are acetaminophen and isoniazid (a drug used to treat tuberculosis).

Nephrotoxicity

Nephrotoxicity is a serious adverse effect that occurs in the kidney. Nonsteroidal anti-inflammatory drugs such as ibuprofen and naproxen can produce nephrotoxicity.

Teratogenicity

Many drugs administered to mother are capable of crossing the placenta & affecting the fetus, likely to be found in mother's milk and could harm the infant. Drugs administered to pregnant women, particularly during the first trimester (3 months), may cause **teratogenic** effects.

A teratogen is any substance that causes abnormal development of the fetus leading to a severely deformed fetus. Drugs known to produce teratogenicity include thalidomide, cyclophosphamide, methotrexate, tetracyclines, phenytoin, carbamazepine and progestogens. Drugs which may be teratogenic e.g Warfarin, lithium, quinine, primaquine, trimethoprim, rifampicin, anesthetic agents.

During pregnancy, the use of all drugs except those essential to maintain pregnancy should be used with caution. Smoking or drinking any type of alcoholic beverage also carries risks, such as low birth weight, premature birth, and fetal alcohol syndrome.

To reduce possible harm to the fetus, pregnant women and their health care providers must weigh the risks versus the benefit of taking drugs. To assist in their decision-making, pregnancy safety categories (see table below) have been created. Drugs with no known teratogenic effects in humans are listed in category A. Drugs known to produce teratogenic effects are listed in category X.

Table 2.3: Pregnancy safety categories

Category	Description
Category A	Both animal and human studies indicate no risk to fetuses.
Category B	Animal reproductive studies indicate no risk; information in humans is reassuring.
Category C	Potential risk reported in animal reproduction studies or no studies conducted. Information in humans is not available. Potential benefits versus risk may warrant the use in pregnant women
Category D	Possible fetal risk in humans reported; however, considering potential benefit versus risk, in selected cases, the use of these drugs in pregnant women may be warranted.
Category X	Fetal abnormalities reported, and positive evidence of fetal risk in humans is available from animal or human studies. These drugs should not be used in pregnant women.

Reading assignment: Read how the factors listed under 2.8 affects drug response and reflect to your trainer during the next session.

2.10.Factors influencing drug response

Individuals differ both in the degree and the character of the response that a drug may elicit and therefore the optimum dose of a drug which produces the desired therapeutic effect varies from person to person. The important factors which influence the effect of a drug are: age, weight, sex, pregnancy, genetics, nutritional status, disease state, drug interaction.

Age

Infants and children usually require smaller doses of a drug than adults do because of immature organ function, particularly the liver and kidneys, can affect the ability of infants and young children to metabolize drugs.

- An infant's immature kidneys impair the elimination of drugs in the urine.
- Liver function is poorly developed in infants and young children.
 - Drugs metabolized by the liver may produce more intense effects for longer periods.
- Like children, old people also present problems in dosage adjustment and this may vary widely with different people.
 - The metabolism of drugs may diminish in the elderly and the renal function declines with age
 - Elderly are sensitive to the drugs like hypnotics, phenylbutazone, diazepam, pethidine etc

Body weight

The average dose is mentioned either in terms of mg per kg body weight or as the total single dose for an adult weighing between 50-100kg. However, a drug dose may sometimes be increased or decreased because the patient's weight is significantly higher or lower than this average. Dose adjustments may need to be considered for obese or severely underweight adults. Drug doses must be increased in obese patients to produce therapeutic effects. Doses are decreased in severely underweight adults and children to avoid toxic side effects.

The pediatric doses are expressed in terms of body weight (mg/kg per dose or day) or in terms of body surface area (mg/m²per day). The body surface area can be calculated from the height and weight of the child

^a Young's rule, based on age:

$$\frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose} = \text{Dose for child}$$

Cowling's rule:

$$\frac{\text{Age at next birthday (in years)} \times \text{Adult dose}}{24} = \text{Dose for child}$$

Fried's rule for infants:

$$\frac{\text{Age (in months)} \times \text{Adult dose}}{150} = \text{Dose for infant}$$

Clark's rule, based on weight:

$$\frac{\text{Weight (in lb)} \times \text{Adult dose}}{150 \text{ (average weight of adult in lb.)}} = \text{Dose for child}$$

Sex

Women may require a smaller dose of some drugs than men. This is because many women are usually smaller than men and have a body fat-and-water ratio different from that of men. The fat-to-muscle ratio varies between women and men and may influence the volume of drug distribution. Additionally, the rate of metabolism of some drugs varies between men and women, suggesting the sex hormones may influence metabolism.

Pregnancy

Drug response may be altered during pregnancy because of pregnancy-related physiological changes. Gastrointestinal (GI) motility slows, which can increase drug absorption and drug effects. The effects of pregnancy-related increases in blood volume, urination, and vomiting may alter drug absorption, distribution, and elimination that result in decreased drug response.

Disease state

Both hepatic (liver) and renal (kidney) disease can greatly affect drug response. In liver disease, for example, the ability to metabolize or detoxify a specific type of drug may be impaired. Lowering dose or lengthening the time between doses might be required. Patients with kidney disease may exhibit drug toxicity and a longer duration of drug action. The dosage of drugs may be reduced to prevent the accumulation of toxic levels in the blood or further injury to the kidney.

Nutritional status

Low-protein diets and diets deficient in essential fatty acids can reduce the synthesis of drug-metabolizing enzymes and decrease metabolism. Deficiencies of vitamins and minerals can affect metabolism because they catalyze biochemical reactions in the body. For example, vitamin B2 catalyzes oxidation reduction reactions. Oxidation and reduction are metabolic processes that result in drug inactivation. Foods can influence metabolism of drugs. Many drug interactions are linked to consumption of grapefruit juice. Grapefruit juice is an inhibitor of metabolic enzyme CYP3A4. When drugs that have a CYP3A4 substrate, such as the anticholesterol drug lovastatin and the antiretroviral drug saquinavir, are taken with grapefruit juice, metabolism is reduced, and blood levels of the drugs can increase along with drug effects.

Genetics

Genetics influence enzyme and protein production in the body. Absence of certain enzymes can produce severe side effects in people who take drugs that require the enzyme for metabolism and elimination. E.g. primaquine causes hemolytic anemia in patients with glucose-6-phosphate dehydrogenase enzyme deficiency.

Drug interaction

Drug interaction is a phenomenon that occurs when the effects of one drug are modified by the prior or concurrent administration of another drug(s), food or herbs which could be beneficial or non-beneficial.

Drug interactions occur because patients frequently take more than one drug.

- They may take multiple drugs to treat a single disorder.
- They may have multiple disorders that require treatment with different drugs.

Drugs can interact through two major mechanisms: Pharmacokinetic and pharmacodynamics interaction.

Pharmacokinetic interaction: when two drugs are taken together, one may alter the absorption, distribution, metabolism, or excretion of the other.

Altered absorption:

- For example, taking an antacid with oral tetracycline causes a decrease in the effectiveness of the tetracycline.
- The antacid chemically interacts with the tetracycline and impairs its absorption into the bloodstream, thus reducing the effectiveness of the tetracycline.

Altered distribution:

- One drug can alter the distribution of another by competition for protein binding
- When two drugs bind to the same site on plasma albumin, co-administration of those drugs produces competition for binding.
- As a result, binding of one or both agents are reduced, causing plasma levels of free drug to rise.

Altered metabolism

- Is one of the most important—and most complex—mechanisms by which drugs interact.
- Some drugs increase the metabolism of other drugs, and some drugs decrease the metabolism of other drugs.
- Drugs that increase the metabolism of other drugs do so by inducing synthesis of hepatic drug metabolizing enzymes.
 - Inducing agents include but not limited to: phenobarbital, carbamazepine, phenytoin and rifampicin.
 - For example, if a woman taking oral contraceptives were to begin taking phenobarbitone, induction of drug metabolism by phenobarbitone would accelerate metabolism of the contraceptive, thereby lowering its level.
 - ▶ To maintain contraceptive efficacy, dosage of the contraceptive should be increased.
- Drugs that decrease the metabolism of other drugs do so by inhibiting those enzymes.
 - Examples of inhibitors include: Ketoconazole, metronidazole, cimetidine, erythromycin.
 - when an inhibitor increases the level of another drug, the outcome is toxicity.
 - Accordingly, when a patient is taking an inhibitor along with his or her other medicines, you should be alert for possible adverse effects.

Altered renal excretion

- Competition between two drugs for active tubular secretion can decrease the renal excretion of both agents.
 - E.g. Penicillin +probenecid

Pharmacodynamic interaction: Occurs at the level of receptors and beyond and it is of great clinical significance.

Drug-drug interactions can produce effects that are **additive, synergistic, antagonistic or potentiation.**

Additive

- occurs when the combined effect of two drugs is equal to the sum of each drug given alone
- Example: The sleeping pill lorazepam is administered to promote drowsiness. Alcoholic beverages also cause drowsiness. When alcoholic beverages are consumed together with lorazepam, additional drowsiness is caused. The sedation caused by lorazepam adds to the sedation caused by alcohol.
- Additive effects can be described using the equation: $1+1=2$

Synergistic

- Occurs when drugs interact with each other and produce an effect that is greater than the sum of their separate actions
- Eg. Trimethoprim + sulfamethoxazole
- Synergistic effects can be described using the equation: $1+1=3$

Antagonistic

- Occurs when one drug interferes with the action of another, causing neutralization or a decrease the effect of one drug.
- For example, Naloxone is administered to block the respiratory depression produced by morphine and heroin.
- Antagonism can be described using the equation: $1+1=0$

Potentiation

- One drug or food increases the effects of another drug, which does not produce any effect when administered alone.
- Potentiation can be described using the equation: $1+0=2$
- Example 1: Carbidopa exhibits no anti-Parkinson disease activity when administered alone. When added to levodopa, the anti-Parkinson disease effects of levodopa are increased. Carbidopa is able to decrease the destruction of levodopa in the gastrointestinal tract so more of the levodopa can get to its site of action in the brain.
- Example 2: The action of the antifungal griseofulvin is increased when it is taken with fatty foods because food increases the absorption of the drug.

Drug-Food Interactions

When a drug is given orally, food may impair or enhance its absorption.

- Some drugs (e.g., captopril) must be taken on an empty stomach to achieve an optimal effect. Drugs that should be taken on an empty stomach are administered 1 hour before or 2 hours after meals.
- Other drugs, especially drugs that irritate the stomach, result in nausea or vomiting, or cause epigastric distress, are best given with food or meals. This minimizes gastric irritation. The nonsteroidal anti-inflammatory drugs and salicylates are examples of drugs that are given with food to decrease epigastric distress.
- Other drugs combine with a drug forming an insoluble food-drug mixture. For example, when tetracycline is administered with dairy products e.g.milk, a drug-food complex is formed that is unabsorbable by the body.

Practice questions: Choose the best answer for the following questions.

1. Which of the following drugs is obtained from a plant?
a. atropine b. insulin c. iron sulfate d. heparin
2. The official, non-proprietary, name of a drug is the
a. Generic name b. Brand name c. Chemical name
3. The process that involves the movement of drug molecules from the site of administration, across cell membranes into the circulatory system of the body is known as
a. distribution b. metabolism c. absorption d. elimination
4. Drugs are assigned to one of five categories according to their safety if taken during pregnancy. Which one of the following is the safest?
a. category A b. category C c. category D d. category X
5. The metabolism of drugs via biochemical processes involving enzymes to metabolites is termed
a. bioequivalence b. biotransformation c. bioavailability d. bioeffect
6. A drug that is administered in an inactive form and must be metabolized to its active form is called a(an)
a. Investigational drug b. metabolite c. prodrug d. none of the above
7. Which body organ serves as the primary site of the metabolism of drugs?
a. kidney b. lungs c. stomach d. liver
8. An _____ is a drug that binds to a receptor site and elicits cellular response.
a. agonist b. antagonist c. alternative d. antimetabolite
9. An adverse effect produced by drugs on fetuses is called _____.
a. carcinogenic b. teratogenic c. pathogenic d. toxic
10. One drug that has a narrow therapeutic index is _____.
a. acetaminophen b. penicillin c. digoxin d. ceftriazone
11. If two drugs with the effect taken together and produce an effect that is equal in magnitude to the sum of the effects of the drugs given individually, the interaction is known as
a. Antagonism b. Additive effect c. Potentiation
12. The component of dosage form which is responsible for a drug's therapeutic effect
a. Inert ingredient b. active ingredient

13. A small solid medicated dosage, usually cone shaped, that is inserted either into the rectum or vagina is
- a. Tablet b. suppository c. capsule d. enema
14. Advantages of oral route of drug administration include
- a. Action slower and thus not suitable for emergencies
 - b. easy to carry and administer
 - c. suitable for Emergency
15. Which of the following is **not** an oral formulation?
- a. Tablet b. Capsule c. Cream d. Syrup

3. Autonomic nervous system (ANS) pharmacology

Dear trainees, at the end of this chapter, you will be able:

- ✚ Discuss the divisions of the peripheral nervous system and its functions
- ✚ List neurotransmitters important to the autonomic nervous system
- ✚ Describe the mechanism of action, clinical uses and common side effects of the following categories of drugs
 - Cholinergic agonists
 - Cholinergic antagonists
 - Adrenergic agonists
 - Adrenergic antagonists

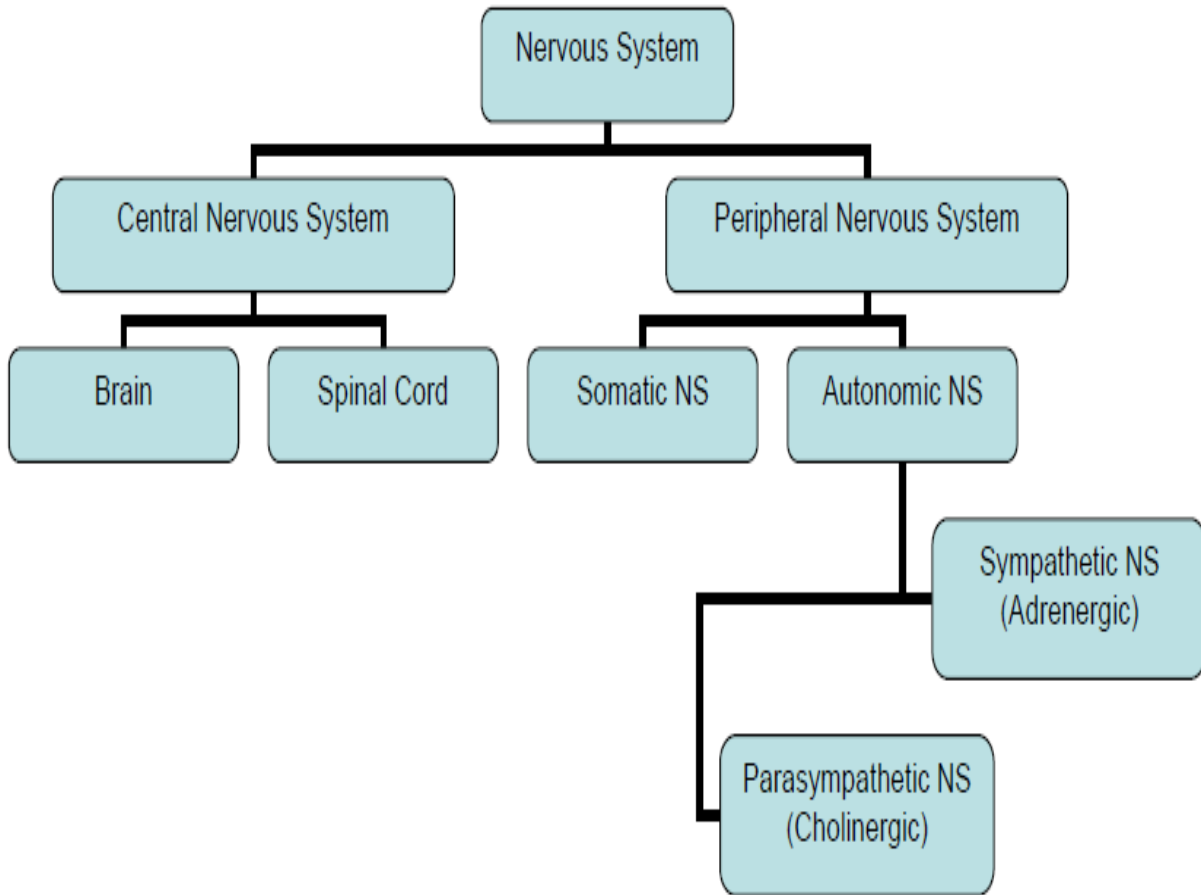
1.1. Introduction to nervous system

Nervous system, or the body's system of communication, is the most complex of the body organ systems. The neuron (nerve cell) is the basic functional unit in this system. There over 100 billion neurons in the brain alone. Neurons also transmit information from the brain to the entire body. The primary parts of this system are the brain and the spinal cord, called the central nervous system (CNS). The peripheral nervous system is composed of nerves that branch out from the spinal cord.

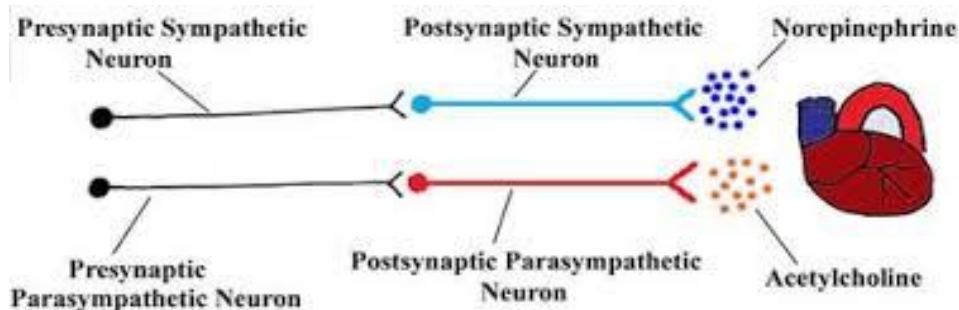
There are subdivisions of the peripheral nervous system called the somatic nervous system and the autonomic nervous system. The autonomic nervous system controls the automatic (involuntary) functions of the body, e.g., breathing, digestion, heartbeat, etc. The somatic nervous system controls the voluntary actions of the body, e.g., skeletal muscle movements.

The ANS is further divided on anatomic grounds into two major portions:

- Sympathetic nervous system
- Parasympathetic nervous system



ANS have two neurons from CNS to the effector tissue. They are called **presynaptic** and **postsynaptic**. The place where the two neurons are connected and communicate with each other is called synapse. Hence synapse is the junction between two neurons, or between a neuron and an effector organ (muscle or gland).

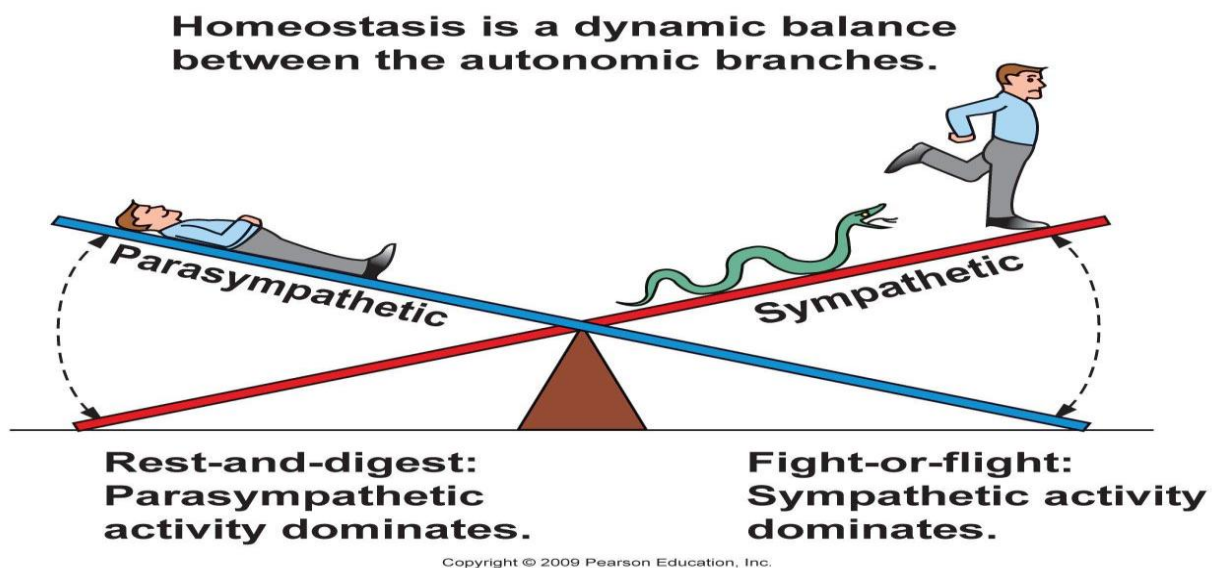


Functions of ANS

ANS system controls the body's internal organs. It innervates smooth muscles, cardiac muscle, and glands, controlling the circulation of blood, activity of the gastrointestinal tract and body temperature.

Autonomic nervous system is involuntary, that is, the function of sympathetic and parasympathetic nerves cannot be influenced by our mind.

Sympathetic and parasympathetic systems have opposing actions in some situations (e.g. control of heart rate), but not in others (e.g. salivary glands). Sympathetic activity increases in stress ('**fight or flight**'), whereas PNS activity predominates '**rest & digest**'. Both systems exert a continuous physiological control of specific organs under normal conditions.



Fight or flight vs. Rest and Digest

ORGAN	SYMP.	PARASYMP.
Heart	↑ rate and force	↓ rate and force
Blood vessels	mostly constriction (dilates some skeletal muscle arterioles and some veins)	no effect
Airway smooth muscle	dilatation	constriction
GI tract	↓ motility	↑ motility
Male sex organs	ejaculation	erection
Eye (pupil)	dilatation	constriction
Salivary glands	secretion	secretion
Liver	glycogenolysis	no effect

Neurotransmitters in autonomic nervous system

Neurotransmitters are chemical substances that are used for the transmission of information between nerve cells and between nerve cells and their effector cells. Acetylcholine and Norepinephrine (noradrenaline) are the major autonomic neurotransmitters. Neurons that release norepinephrine are known as adrenergic neurons. Norepinephrine binds to adrenergic receptors. neurons that release acetylcholine are known as cholinergic neurons. Acetylcholine binds to cholinergic receptors.

Cholinergic receptors

Acetylcholine binds to cholinergic receptors. Cholinergic receptors are classified into muscarinic and nicotinic cholinergic receptors. Cholinergic receptors have subtypes, such as nicotinic 1 (N1), nicotinic 2 (N2), muscarinic 1 (M1), and muscarinic 2 (M2). The action of ACh is quickly terminated through hydrolysis by the enzyme acetylcholinesterase.

Adrenergic receptors

Receptors that respond to adrenergic nerve transmitter are termed adrenergic receptors. These receptors are subdivided into alpha and beta adrenoreceptor types on the basis of both agonist and antagonist selectivity. The receptors have subclasses depending on drug selectivity. These are alpha 1 and 2 and beta 1, and 2.

The binding of norepinephrine to alpha receptors in the smooth muscle of blood vessels has a stimulating effect on the muscle that causes the muscle to constrict. The binding of norepinephrine to beta receptors in the smooth muscle of a different blood vessel produces opposite effects. The binding of norepinephrine to beta receptors in cardiac muscle has a stimulating effect that results in a faster and stronger heartbeat. The actions of norepinephrine and epinephrine are terminated in two ways. Most of the neurotransmitter molecules are taken back up by the synaptic knob of the postganglionic neurons, where they are broken down by the enzyme monoamine oxidase (MAO). The remaining neurotransmitter molecules are eventually broken down by another enzyme, catechol-O-methyltransferase (COMT).

1.2. Cholinergic agonists

Cholinergic agonists can be divided into directly and indirectly acting drugs.

- Direct-acting (agonist)
 - Bind to cholinergic receptors, causing stimulation
- Indirect-acting
 - Inhibit the enzyme “cholinesterase” and prolong the effect of endogenous acetylcholine

Directly acting cholinergic agonists

- Cholinergic agonists mimic the effects of ACh by binding directly to muscarinic or nicotinic.
- These agents may be broadly classified into two groups:
 - choline esters which include ACh and synthetic esters of choline, such as carbachol and bethanechol, and

- naturally occurring alkaloids, such as nicotine and pilocarpine

Pilocarpine

- is a directly acting muscarinic agonist and used for the treatment of glaucoma (a disease with enhanced pressure of fluid in the eyeball).
- Pilocarpine constricts the ciliary muscle in the eye, which promotes the outflow of intraocular fluid through the canal of Schlemm

Bethanecol

- has mainly muscarinic actions
- Relaxes sphincters in bladder and GI tract, allowing them to empty
- Helpful for postsurgical atony of the bladder and GI tract
- Dose: 10-40 mg oral, 2.5-5.0 mg SC

Carbachol

- is a direct agonist of both muscarinic and nicotinic receptors
- It is useful only as an eye drop to treatment of glaucoma as second line drug next to pilocarpine.

Adverse effects

Adverse effects of cholinergic agonists are practically muscarinic types:

- bronchoconstriction, bradycardia, increased gastric acid secretion, sweating, difficulty in visual accommodation, increased salivation.

Indirectly acting cholinergic agonists

Indirectly acting drugs, logically, do not directly act on the receptor. They inhibit the acetylcholine esterase enzyme (AChE) and thus, these drugs do not mimic but increase both the level and duration of the neurotransmitter.

According to the mode of action, AChE inhibitors can be divided into two groups: **irreversible and reversible**.

Reversible inhibitors

Edrophonium

- It is used for diagnosis of Myasthenia gravis

- Since it has a very short duration of action not for the treatment of myasthenia gravis

Neostigmine: is a reversible AchE inhibitor and used for the treatment of:

- Myasthenia gravis treatment (nicotinic action).
- Paralytic ileus (like bethanechol which is direct drug)
- Urinary retention
- Competitive (non-depolarizing) neuromuscular blockers intoxication

Physostigmine

- is lipid soluble (non-polar) reversible AchE inhibitor used for the treatment of Glaucoma and Atropine toxicity (anti-muscarinic drug).

Donepezil, Rivastigmine, and Galantamine: used in treatment of Dementia of Alzheimer's disease

Irreversible inhibitors

- The result is a long-lasting increase in ACh at all sites where it is released
- Many of these drugs are extremely toxic and were developed by the military as nerve agents.
- Related compounds, such as parathion and Malathion, are used as insecticides.
- **Ecothiopate:** are topical eyedrops only for the treatment of severe glaucoma.

Adverse effects: (same for both direct and indirect cholinomimetics)

Mnemonics (reminders) helpful to remember the **muscarinic** (mostly parasympathetic) peripheral effects of cholinesterase inhibitors are **DUMBBELLS**:

- **D**iarrrhea (Diaphoresis), **U**rination, **M**iosis, **B**ronchospasm (secretion) **B**radycardia, **excite** skeletal muscle and CNS (**E**mesis), **L**acrimation, **L**ethargy, **and Salivate**

Mnemonic for remembering the **nicotinic** signs of cholinesterase inhibitor toxicity

M onday	M ydriasis (pupillary dilation)
T uesday	T achycardia
W ednesday	W eakness
T hursday	H ypertension
F riday	F asciculation

Contraindications: (same for both direct and indirect cholinomimetics)

- Both direct and indirect cholinomimetic drug should not be given for those patients with the following clinical problem:
 - Bronchial asthma
 - Peptic ulcer
 - Angina pectoris
 - urine incontinence
 - Intestinal obstruction

1.3. Cholinergic antagonists

Cholinergic antagonist is a general term for agents that bind to cholinceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists. Nicotinic receptor blockers are ganglionic blocking drugs or neuromuscular blockers (skeletal muscle relaxants) depending on the location of the nicotinic type acetylcholine receptors.

Antimuscarinic agents

- Antimuscarinic are drugs which block ACh at the muscarinic receptors in the PSNS
- Drugs include: Atropine, Scopolamine (Hyoscine), Ipratropium bromide, Benztropine, Trihexyphenidyl

Therapeutic uses

- Parkinson's disease: Benztropine, Biperiden, Procyclidine & Trihexyphenidyl used as adjunctive therapy
- Motion sickness: Scopolamine (oral or transdermal prophylactically 4 hrs. before journey)
- As Anti-secretory and Preanesthetic medication: Atropine used for this purpose
- Urinary incontinence: Tolterodine is M3 selective drugs used to relieve urinary frequency, and urgency and Enuresis in children
- Asthma: Ipratropium bromide is used as inhalational drug in asthma.

- Chronic obstructive pulmonary disease (COPD) patients – Chronic smokers, older patients: Tiotropium bromide a long acting quaternary anti-muscarinic drug and can be given once daily.
- Bradycardia and partial heart block: Atropine is useful if these cases are occurred
- Abdominal cramp and intestinal colic: Dicyclomine is good drug for this purpose
- Non- infectious, traveler and drug induced diarrhea: atropine (usually used in combination with diphenoxylate)
- To reverse the toxicity of organophosphate (irreversible cholinesterase inhibitors) poisoning: IV atropine sulfate every 5-15 min until signs of toxicity reversed.

Adverse effects

- Dry mouth, mydriasis, blurred vision tachycardia, dry eyes, hot & flushed skin, body temperature increases, constipation, hallucinations, agitation, delirium which may progress to depression, collapse of circulatory and respiratory system, coma and death.
- Simply the adverse effects of muscarinic blocker are anti- **DUMBBELLS**.

Contraindication of Antimuscarinic drugs

- Avoid the use of anti-muscarinic drug in glaucoma patients especially angle closure, and with a history of prostatic hyperplasia and use in elderly men with caution.

Anti-nicotinic drugs

Two types: ganglion blockers and neuromuscular blockers

Ganglionic blockers

Ganglionic blockers act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. Since responses observed are complex and unpredictable they are rarely used therapeutically.

Neuromuscular blockers

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle. These Nm blockers are structural

analogs of acetylcholine, and act either as antagonists (non- depolarizing type) or, as agonists (depolarizing type) receptors on the end plate of the Nm junction.

i. Non-depolarizing (competitive) blockers

- E.g. tubocurarine, cisatracurium, pancuronium, rocuronium, and vecuronium
- Used during surgery to relax muscles combined with anesthetics
 - Increase safety of anaesthetics by reducing the dose of anesthetics required
- Injected intravenously, as oral absorption is minimal
- Penetrate the membrane very poorly and do not enter cells or cross the BBB

ii. Depolarizing blockers

- Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh.
- However, these agents are more resistant to degradation by acetylcholinesterase and can thus more persistently depolarize the muscle.
- **E.g. Succinylcholine**

Therapeutic uses: Because of its rapid onset of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia

Adverse effects: Malignant Hyperthermia (caused by abnormal release of calcium from stores in skeletal muscle), apnea and hyperkalemia.

Practice exercise: Match drugs listed under column 'A' with their indications listed under column 'B'.

A

1. Pilocarpine
2. Neostigmine
3. Bethanechol
4. Hyoscine
5. Ipratropium
6. Atropine

B

- A. Motion sickness
- B. Preanesthetic drug
- C. Asthma
- D. Myasthenia gravis
- E. Post-surgical GI atony
- F. Glaucoma

I. Case study

A young lady named AB has been brought to the emergency department of Jimma university medical center. She is sweating heavily, vomiting, and having difficulty in breathing. She cannot walk without assistance, and she has a reduced heartbeat. She is delirious and unable to explain her condition. The friend who brought her in said, she had ingested some household chemical trying to commit suicide.

Answer the following questions based on the above case.

1. What would be the most likely chemical ingested?
2. What would be the mechanism of action of the poisoning chemical?
3. What drug do you recommend for AB in management of her condition?

1.4. Adrenergic agonists

- Drugs that stimulate the sympathetic nervous system (SNS)
- Also known as adrenergic agonists or sympathomimetics
- Mimic the effects of the SNS neurotransmitters: norepinephrine (NE) and epinephrine (EPI)

Effects of adrenoceptor activation**Table 3.1.** Adrenoceptor subtypes and their function

Type	Tissue	Action
Alpha₁	Most vascular smooth muscles	Contraction
	Pupillary dilator muscle	Mydriasis
	Heart	Increase force of contraction
Alpha₂	Adrenergic nerve terminals	Inhibition of transmitter release
	platelets	Aggregation
Beta₁	Heart	Increase rate and force of heart contraction
Beta₂	Respiratory, uterine, and vascular smooth muscles	Relaxation
	Human liver	Glycogenolysis
Beta₃	Fat cell	Lipolysis

The sympathomimetic classified by mode of action into three groups

Direct acting

- Act directly interact with and activate one or more of the adrenergic receptors
- e.g., norepinephrine and epinephrine

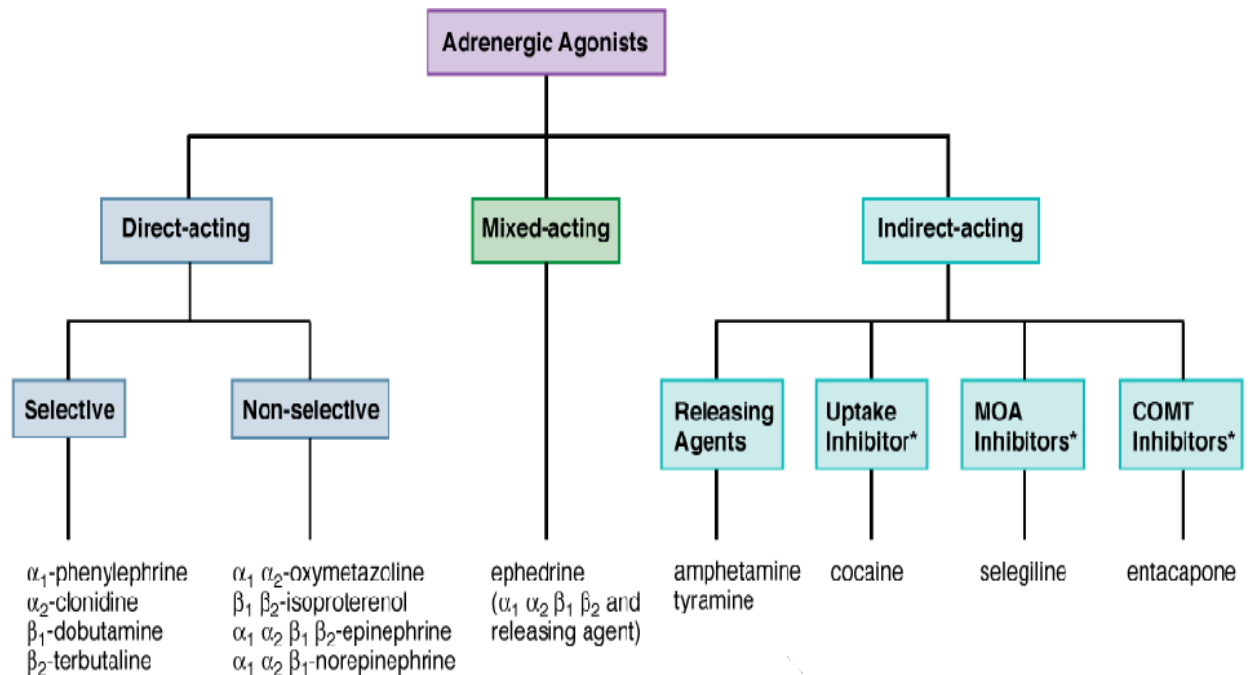
Indirect acting

- Increase the availability of norepinephrine or epinephrine to stimulate adrenergic receptors by
 - causing displacement of stored catecholamines from adrenergic nerve endings (e.g., Amphetamine and tyramine) or

- inhibition of reuptake of already released catecholamines from the synapse (e.g., Cocaine and tricyclic antidepressants (TCADs))
- Blocking the metabolizing enzymes: e.g. Monoamine oxidase (MAO) is inhibited by pargyline while catechol-O-methyltransferase (COMT) is inhibited by entacapone

Mixed acting sympathomimetics

- Refers drugs that indirectly release norepinephrine and also directly activate adrenoreceptors. e.g., ephedrine, dopamine



Epinephrine (adrenaline)

- Epinephrine interacts with both α and β receptors.
- At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effect (vasoconstriction) is the strongest.

Therapeutic uses of epinephrine

- **Bronchospasm:** in treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice and can be lifesaving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves.
- **Anaphylactic shock:** Epinephrine is the drug of choice for the treatment of types I hypersensitivity reactions (including anaphylaxis) in response to allergens.

- **Cardiac arrest:** Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest.
- **Anesthetics:** Local anesthetic solutions may contain low concentrations Epinephrine greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection.
- This allows the local anesthetic to persist at the injection site before being absorbed into the systemic circulation.

Epinephrine Side Effects

- Nervousness, tremor, insomnia Paradoxical bronchospasm, Angina, arrhythmias, Hypertension, Tachycardia Nausea/Vomiting and Hyperglycemia

Dopamine

- At low rates of infusion
 - D₁-mediated vasodilation in renal, coronary vessels with little effect on other blood vessels or on the heart.
- At higher rates of infusion
 - It causes β_1 -mediated increased force of heart contraction and α_1 - mediated generalized vasoconstriction
- Indications
 - Treatment of severe congestive failure
 - Treatment of cardiogenic and septic shock.

Selective alpha 1 agonists

- **E.g. Phenylephrine**
- Phenylephrine causes marked arterial vasoconstriction during intravenous infusion.
- Phenylephrine is used as a nasal decongestant and as a mydriasis in various nasal and ophthalmic formulations.

Alpha 2 selective agonists: methyldopa and clonidine

Methyldopa

- Centrally acting antihypertensive agent (it is the preferred agent during pregnancy)
- Causes activation of central alpha₂ receptors
- Inhibits SNS activity and leads to a fall in Blood pressure

- **Adverse effects:** sedation, dry mouth, bradycardia, hepatotoxicity, hemolytic anemia

Beta 1-selective agonists E.g. Dobutamine

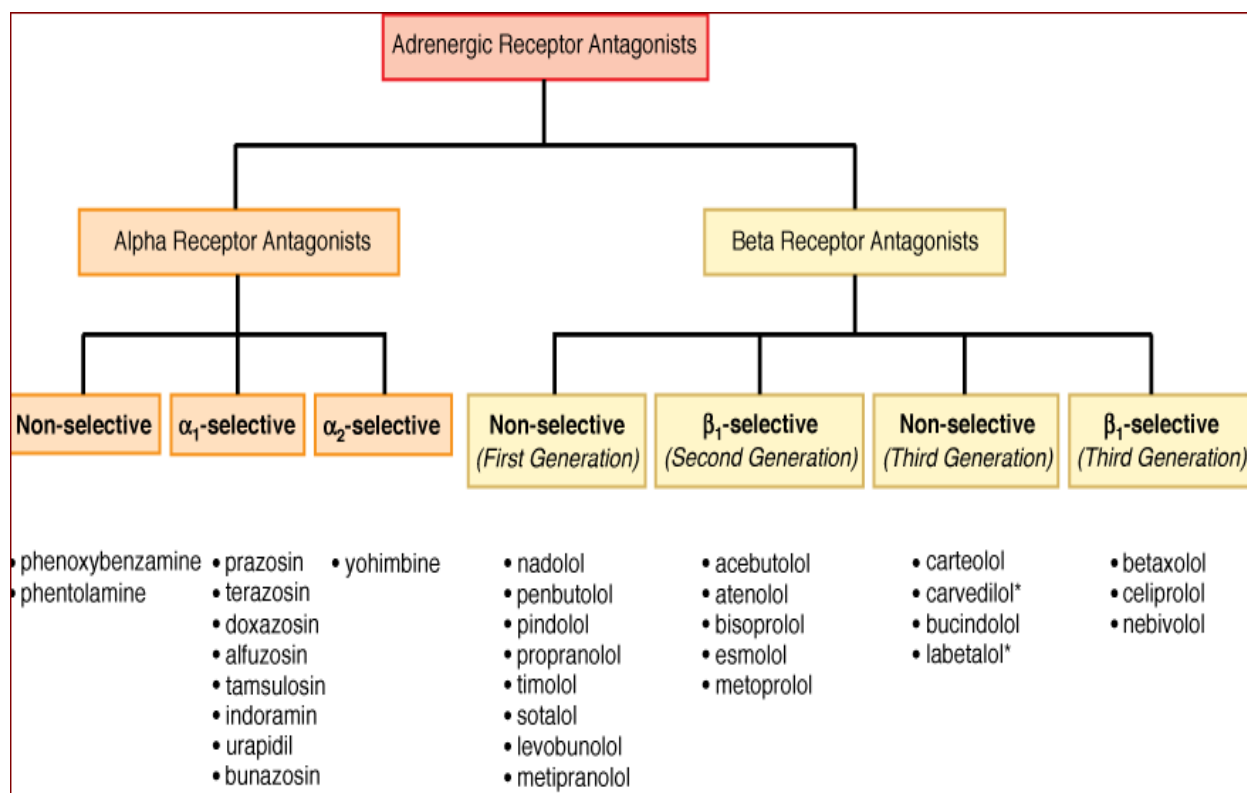
- Dobutamine injection is used for treatment of heart failure, shock and atrioventricular heart block
- Adverse Effects of Beta1 Activation: tachycardia (excessive heart rate), dysrhythmias (irregular heartbeat) and Angina Pectoris.

Beta 2 selective agonists

- Used for treatment of asthma
- Classified into two based on the duration of action
 - Short acting:** Albuterol and terbutaline are short-acting β_2 agonists.
 - Albuterol is the short acting β_2 agonist of choice for the management of acute asthma symptoms.
 - Long acting:** Salmeterol and formoterol are long acting β agonists (LABAs) that are β_2 selective.
 - Salmeterol and formoterol are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.
- **Adverse Effects**
 - Tremor is a relatively common adverse effect
 - Can be minimized by starting oral therapy with a low dose of drug and progressively increasing the dose as tolerance to the tremor develops.
 - Feelings of restlessness, apprehension, and anxiety
 - Tachycardia is a common adverse effect with systemic administration

1.5. Adrenergic antagonist

The adrenergic antagonists (also called adrenergic blockers or Sympatholytic) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines



Alpha-adrenergic blocking agents

The adrenergic antagonists (also called adrenergic blockers or sympatholytic) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. As indicated in the flow chart above adrenergic blockers are classified into selective and non-selective based on their affinity toward either beta1 or beta 2 receptors.

Non-Selective α-Adrenergic Receptor Antagonists:

- Non-selective Alpha-receptor antagonists may be reversible (**Phentolamine**) or irreversible (**Phenoxybenzamine**) in their interaction with these receptors.

Therapeutic Uses: both drugs are used in the following condition

- Treatment of pheochromocytoma
- Treat patients in preparation for surgery
- Prolonged treatment in patients with inoperable or malignant pheochromocytoma
- Erectile dysfunction

Toxicity and adverse effects

- Postural hypotension accompanied by reflex tachycardia, reversible inhibition of ejaculation.

α_1 -Adrenergic Receptor Selective Antagonists

- Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin are selective competitive blockers of the α_1 receptor
 - Inhibits vasoconstriction induced by endogenous catecholamines; vasodilation may occur in both arteriolar resistance vessels and veins,
 - Resulting in a fall in blood pressure due to decreased peripheral resistance.
- **Therapeutic use:**
 - Treatment of hypertension (prazosin, terazosin, doxazosin)
 - Congestive heart failure
 - Benign prostatic hyperplasia (especially Tamsulosine)
- **Adverse effects**
 - Most common side effect is postural hypotension and syncope when administered for the first time (“first- dose phenomenon”).
 - This disappears with continued therapy, tolerance develops and cardiovascular reflexes are not impaired appreciably by chronic therapy.
 - Other side effects: - headache, drowsiness, dry mouth, blurred vision, stress incontinence

Beta-adrenergic blocking agents

- Block stimulation of beta receptors in the SNS
- Two types
 - Non-selective beta blockers: Propranolol, timolol, nadolol, pindolol
 - Cardioselective (Beta1) blockers: atenolol, esmolol, metoprolol
- **Therapeutic use:**
 - Angina and Certain tachyarrhythmia
 - Myocardial infarction
 - Heart failure

- Hypertension
- Glaucoma (topical use): reduce production of aqueous humor
 - Eg. timolol
- Hyperthyroidism, migraine headache, anxiety: propranolol
- **Adverse effects**
 - Bronchoconstriction: non-selective beta blockers like propranolol
 - Bradycardia
 - Hypoglycemia
- **Contraindication**
 - **Asthma is an absolute contraindication**
 - Insulin-dependent diabetes
 - Masking of hypoglycemia in insulin-dependent diabetes because of blunting of sympathetic nervous activation.

Table: Summary of drugs acting on ANS

Drug	Primary Receptors	Primary Use
Examples of Cholinergics		
bethanechol	Cholinergic	Increase urination
pilocarpine	Cholinergic (eye)	Glaucoma
pyridostigmine	Cholinergic	Myasthenia gravis
galantamine	Cholinergic	Alzheimer's disease
Examples of Anticholinergics		
atropine	Cholinergic	Dilate pupils and increase heart rate
benztropine	Cholinergic	Parkinson's disease
ipratropium bromide	Cholinergic	Asthma
oxybutynin	Cholinergic	Incontinence
scopolamine	Cholinergic	Motion sickness
Examples of Sympathomimetics		
albuterol (salbutamol)	β_2	Asthma
clonidine	α_2	Hypertension
dobutamine	β_1	Cardiac stimulant
norepinephrine	α_1 and β_1	Shock
salmeterol	β_2	Asthma
Examples of Adrenergic Antagonists		
atenolol	β_1	Hypertension
carvedilol	α_1 , β_1 , and β_2	Hypertension
doxazosin	α_1	Hypertension
propranolol	β_1 and β_2	Angina and hypertension
terazosin	α_1	Benign prostatic hypertrophy and hypertension

Practice Exercise: Match adrenergic drugs listed under column 'A' with their specific classes under column 'B'.

A.

1. Epinephrine/adrenaline
2. Propranolol
3. Prazosin
4. Phenylephrine
5. Salbutamol
6. Atenolol
7. Dobutamine
8. Timolol
9. Carvedilol
10. Methyldopa

B.

- A. Centrally acting alpha 2 agonist
- B. Non-selective adrenergic agonist
- C. Non-selective beta antagonist
- D. Selective beta 1 blocker(antagonist)
- E. Selective beta 1 agonist
- F. Selective alpha 1 agonist
- G. Selective beta 2 agonist
- H. Non-selective adrenergic antagonist
- I. Selective alpha 1 antagonist
- J. Selective alpha 2 antagonist

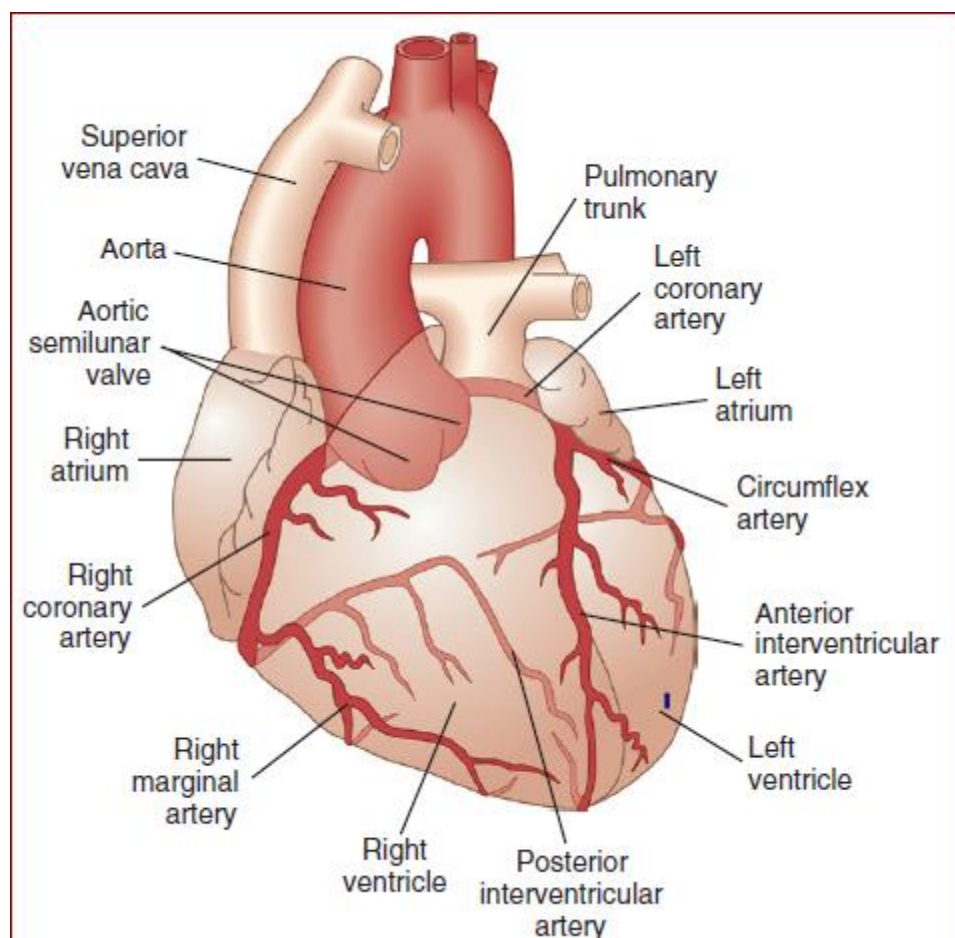
2. Drugs acting on cardiovascular system

Dear trainees, at the completion of this chapter, you will be able to:

-  Describe cardiovascular system and its function
-  Identify common cardiovascular diseases and drugs used to treat the diseases
-  Discuss the common side effects and contraindications of drugs used treat various cardiovascular diseases

2.1. Introduction

The cardiovascular system distributes blood throughout the body using blood vessels called arteries, capillaries and veins. Blood transports nutrients to the body's cells and carries waste products away from them. Blood is made up of red blood cells, white blood cells, platelets, and plasma. Red blood cells (Erythrocytes) transport oxygen from the lungs to the body and carbon dioxide from the cells to the lungs. White blood cells (Leukocytes) fight diseases (infections) by producing antibodies.



Blood is pumped through the cardiovascular system by the heart. Valves within the heart maintain the flow of blood in only one direction. Conductive tissue which is unique to the heart muscle is responsible for the heartbeat.

When blood is forced out of the heart, the increased pressure on the system is called the systolic phase. When blood pressure is monitored, this pressure is reported as the first number of the two numbers sequence. The diastolic phase (relaxation phase) is the second number reported in blood pressure monitoring. Blood pressure is reported as systole/diastole, e.g. 120/80.

Arterial blood pressure is controlled by the force of contraction of the heart which determines the amount of blood pumped by the heart knowns cardiac output and the peripheral resistance (resistances in parallel though various vascular beds). The fullness of the circulation is controlled by the kidneys, which play a critical role in essential hypertension.

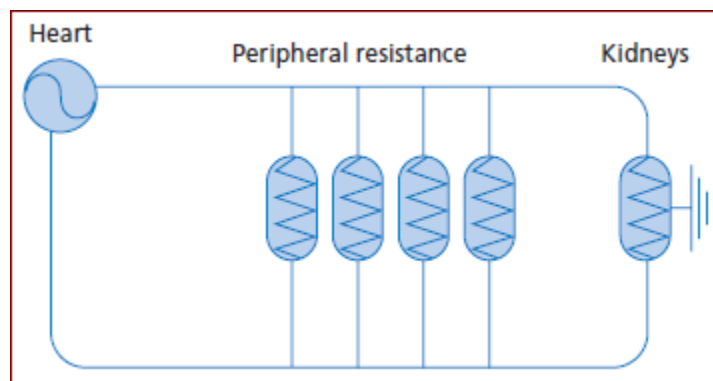


Figure: regulation of blood pressure

The most commonly encountered cardiovascular disorders include:

- Hypertension
- congestive heart failure
- angina pectoris and
- cardiac arrhythmias

2.2. Anti-Hypertensive drugs

What is Hypertension?

Hypertension is defined as systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg.

Table 4.1: Classification of hypertension

Classification	Blood pressure (mmHg)	
	Systolic	Diastolic
Normal	<120	And <80
Pre-hypertension	120-139	Or 80-89
Hypertensionstage1	140-159	Or 90-99
Hypertensionstage 2	≥ 160	Or ≥ 100

There are 2 general types of Hypertension:

Essential Hypertension

- There is an absence of identifiable secondary cause.
- This accounts for ~95% of all cases of hypertension.
- Also referred to as primary or idiopathic hypertension.
- It is a heterogeneous disorder with numerous risk factors including sedentary lifestyle, obesity, insulin resistance (metabolic syndrome), salt/sodium sensitivity, alcohol intake, age, family history.

Secondary Hypertension

- Where hypertension can be attributed to an identifiable cause (e.g. aldosteronism, hyperthyroidism, glucocorticoid excess, renovascular disease, renal failure, pheochromocytoma)
- Treatment is targeted to the underlying cause

Why should we treat hypertension?

Sustained arterial hypertension damages blood vessels in kidney, heart and brain and leads to an increased incidence of renal failure, cardiac failure, and stroke.

Effective pharmacologic lowering of blood pressure prevents the damage to blood vessels and reduces the morbidity and mortality rate.

Treatment of hypertension

Two therapeutic Interventions

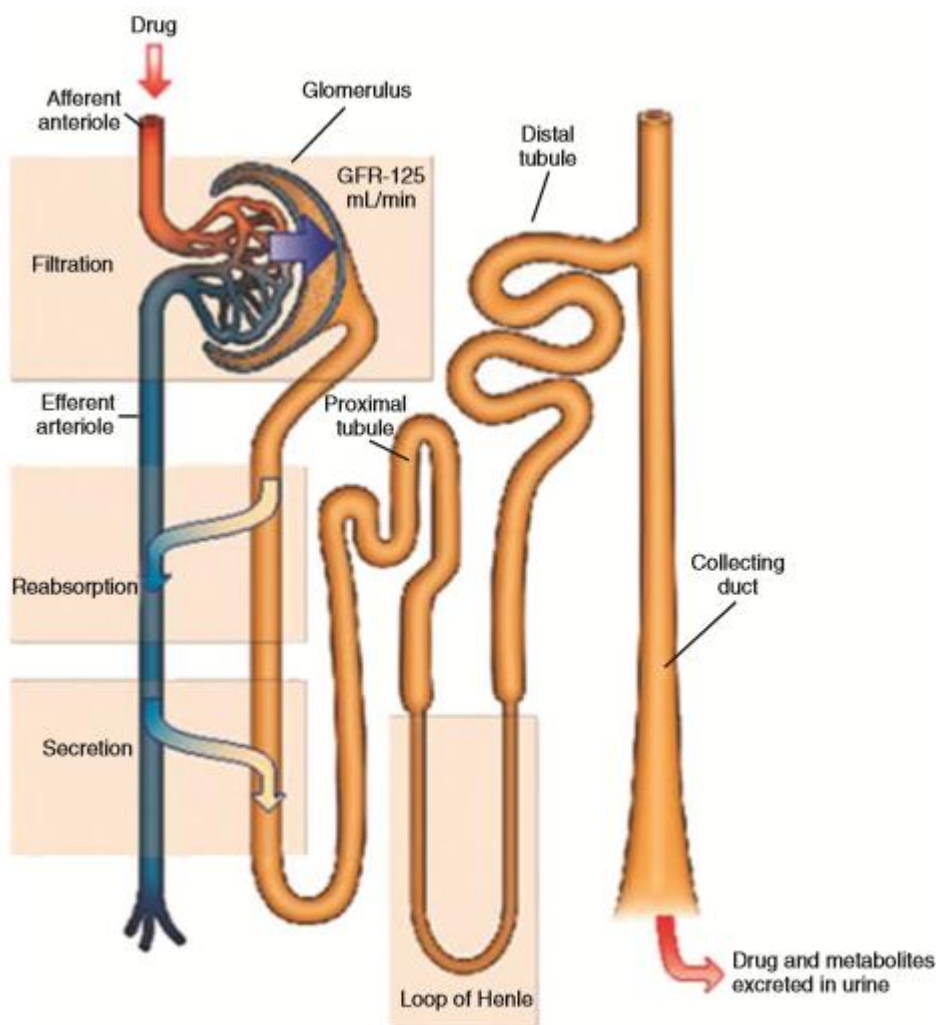
- Non-pharmacologic
- Pharmacologic
 - a. Non- pharmacological therapy of hypertension
- Low sodium chloride diet
- Weight reduction
- Exercise
- Cessation of smoking
- Decrease in excessive consumption of alcohol
- Avoid stress
- b. Pharmacological therapy of hypertension
- Currently available drugs lower blood pressure by decreasing either cardiac output (CO) or total peripheral vascular resistance (PVR) or both
- Anti-hypertensive drugs are classified according to the principal regulatory site or mechanism on which they act into:
 - Beta adrenergic blockers: eg. Atenolol, propranolol, metoprolol, labetalol
 - Alpha blockers: eg. prazosin
 - Centrally acting anti-hypertensive eg. Methyldopa
 - Diuretics
 - Direct vasodilators
 - Angiotensin converting enzyme inhibitors
 - Angiotensin II receptor blockers
 - Calcium channel blockers

Diuretics

Diuretics are drugs that increase the rate of urine formation and Sodium (salt) excretion. The kidneys play a major role in regulating blood pressure, and diuretics exert their effects on the kidneys. The diuretics increase the elimination of water, sodium, and selected electrolytes (K⁺,

Cl⁻, HCO₃⁻), depending on their location of action in the kidney, in the nephrons (see figure below).

Diuretics reduce blood pressure by reducing blood volume and cardiac output as a result of a pronounced increase in urinary water and electrolyte particularly sodium excretion.



Commonly used diuretic classes include: Loop diuretics, thiazide diuretics, and potassium sparing diuretics.

Loop diuretics

- Example: Furosemide, Ethacrynic acid
- Effective in patients with decreased renal function (unlike the thiazides)
- Adverse effects

- anorexia, nausea, vomiting, dizziness, rash, postural hypotension
- Hypokalemia (may cause arrhythmia if given with digoxin)
- Ototoxicity (electrolyte imbalance in the inner ear)
- Hyperuricemia (may precipitate gout)

Thiazide diuretics

- Chlorothiazide, Hydrochlorothiazide
- hydrochlorothiazide is the most widely used thiazide diuretic for hypertension

Potassium sparing diuretics

- e.g. spironolactone
- The diuretic action of these drugs is weak when administered alone
- used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion (hypokalemia)

Direct vasodilators: E.g. hydralazine, sodium nitroprusside

Hydralazine:

- Dilates arterioles but not veins.
- Is used particularly in severe hypertension
- The most common adverse effects are headache, nausea, anorexia, palpitations, sweating and flushing

Sodium nitroprusside:

- It is a powerful vasodilator that is used in treating hypertensive emergencies
- It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return.
- Nitroprusside rapidly lowers blood pressure and it is given by intravenous infusion.
- The most serious toxicities include metabolic acidosis, arrhythmias, excessive hypotension and death.

Angiotensin converting enzyme inhibitors: Captopril, enalapril, etc

- They lower blood pressure principally by decreasing peripheral vascular resistance
- The common adverse effects include
 - The main adverse effect on chronic use is cough;
 - angioedema, cough, first-dose hypotension, and hyperkalemia
 - Are contra-indicated during pregnancy

Angiotensin II receptor blockers (ARBs), eg losartan, candesartan, irbesartan etc

- They lower blood pressure by blocking the binding of angiotensin II. ARBs also inhibit angiotensin II–stimulated growth of smooth muscle, reducing ventricular and arterial hypertrophy that is associated with chronic hypertension.
- The ARBs are similar to ACE inhibitors in effectiveness but produce less dry cough, perhaps because they do not increase bradykinin levels like the ACE inhibitors.
- The ARBs are first-line therapy for treatment of hypertension, especially in patients with diabetes and coronary artery disease who cannot tolerate ACE inhibitors.

Calcium channel blockers e.g. nifedipine, Amlodipine, verapamil

- Lower blood pressure because of their ability to relax blood vessels
- The main adverse effect in chronic use is ankle swelling.
- The most important toxic effects for calcium channel blockers are cardiac arrest, bradycardia, atrioventricular block and congestive heart failure and are contraindicated in such scenarios

Beta-blockers; reduce the risk of vascular events, but are contraindicated in patients with obstructive pulmonary disease. Adverse events (dose-related) include fatigue and cold extremities. Heart failure, heart block or claudication can be exacerbated in predisposed patients.

List of common anti-hypertensive drugs and their dosage

Name	Dose (in mg)
Diuretics, e.g. Hydrochlorthiazide	12.5-25 mg per day
Beta- Blockers, e.g. Atenolol	25-50 mg QD
Calcium channel blockers, e.g. Nifedipine	10-40 mg BID
Anti-adrenergic agents, e.g. Methyl-dopa	250-500 mg BID
ACE Inhibitors, e.g. Enalapril	2.5-40 mg QD

Drugs used in hypertensive crisis

Drug	Route	Initial dose	Dose Range	Onset peak Effects	Duration
Nitroprusside	I.V	0.5 µg/kg per min	0.5 to 10 µg/kg per min	1 to 2 min	2 to 3 min
Hydralazine	I.V	5-10 mg	5 to 20 mg every 20-30 min	5 to 15min	2 to 6 hr
Captopril	P.O	6.25 to 12.5 mg	12.5 - 50 mg every 8 hr	30 to 90 min	4 to 6 hr
Propranolol	I.V	0.5 to 1 mg	0.5 mg every 5 min (maximum 6 mg)	1 to 2 min	4 to 12 hr

4.3. Drugs for Heart Failure (HF)

Heart failure is a syndrome in which the heart is unable to pump sufficient blood to meet the metabolic needs of tissues. It is a highly lethal condition, with a 5-year mortality rate conventionally said to be about 50%. Presenting symptoms are weakness, dyspnea, orthopnea and body swelling.

Drug classes used for heart failure include:

- **Diuretics: furosemide, hydrochlorothiazide, spironolactone**
 - furosemide is drug of choice for patients with severe HF
- **Cardiac glycosides-digoxin**
- **Beta - adrenergic stimulants e.g. dopamine, dobutamine**
- **Angiotensin converting enzyme inhibitors e.g. captopril, enalapril**

Digoxin

- + Digoxin increases myocardial contractile force thereby increase cardiac output
- + Is dangerous drug because, at doses close to therapeutic, it can cause severe dysrhythmias

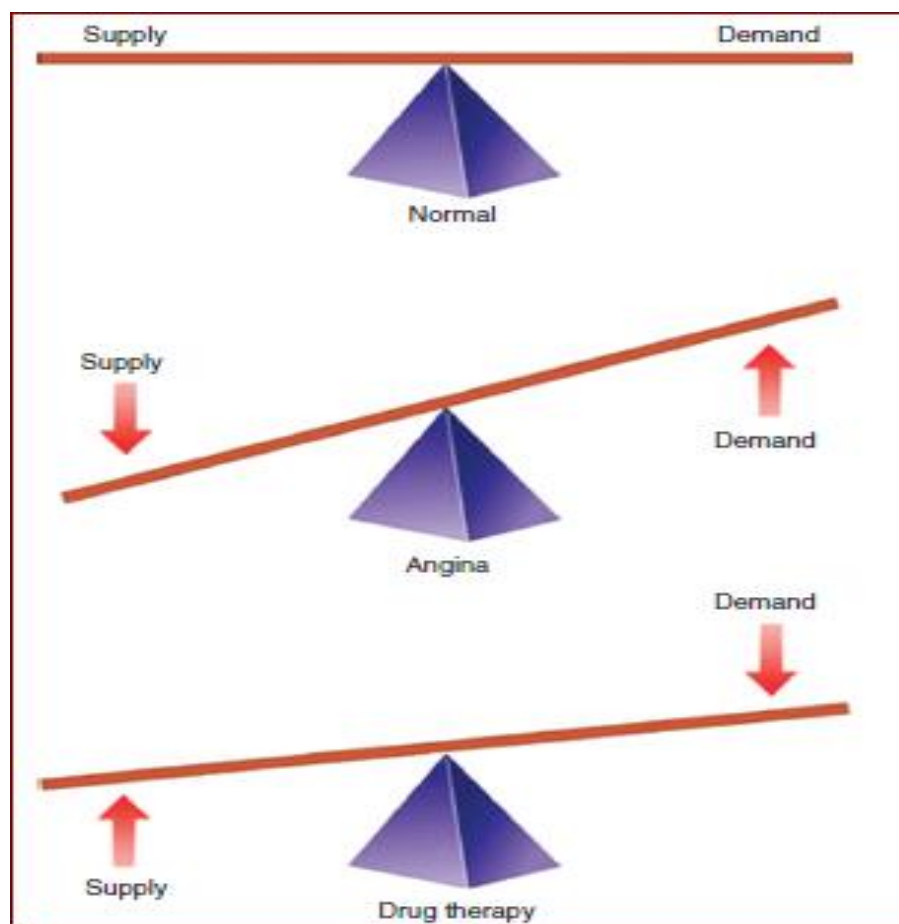
Adverse effects:

- + Anorexia, nausea, and vomiting, Confusion, dysrhythmia
- + Decreased K⁺ increases the potential for cardiotoxicity
 - Reduction of serum potassium levels is most frequently observed in patients receiving thiazide or loop diuretics which can usually be prevented by use of a potassium-sparing diuretic or supplementation with potassium chloride

4.4. Anti-anginal drugs

Angina pectoris

- Is a sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms
- Occurs when oxygen supply to the heart is insufficient to meet oxygen demand
- When the increase in coronary blood flow is unable to match the increased oxygen demand
 - angina develops
- Oxygen supply to the heart is reduced by thrombus and vasospasm
- Oxygen demand is increased when heart rate and contractility increase
- Angina can be treated by drugs that can either increase oxygen supply to the heart or drugs that can decrease oxygen demand of the heart



There are three families of antianginal agents: organic nitrates, Beta blockers, and calcium channel blockers.

Organic nitrates

- Include nitroglycerine, isosorbide dinitrate
- are most frequently used antianginal drugs
- Work by causing vasodilation and thereby increase oxygen supply
- Adverse effects: headache, postural hypotension, facial flushing, Reflex tachycardia

Beta blockers: - propranolol, atenolol

- decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart

Calcium channel blockers: - verapamil, nifedipine

- Cause relaxation of the coronary arteries and thereby increase oxygen supply

- Verapamil can produce modest additional reductions in oxygen demand by suppressing heart rate and contractility

4.5. Drugs for cardiac arrhythmia

Normally, the electrical system of the heart causes it to contract (or beat) in a regular and organized rhythm that can be graphed by an electrocardiogram (EKG). An arrhythmia is an abnormal heart rhythm that can interfere with the heart's ability to pump in an effective, organized manner. Familiar arrhythmias include tachycardia, bradycardia, flutter and fibrillation.

- Antiarrhythmic drugs are used to prevent or correct cardiac arrhythmias

Drugs used in the treatment of cardiac arrhythmias are traditionally classified into:

Class (I): Sodium channel blockers which include quinidine, lidocaine, phenytion, etc.

Class (II): Beta adrenergic blockers which include propranolol, atenolol, etc.

Class (III): Potassium channel blockers e.g. amiodarone, bretylium.

Class (IV): Calcium channel blockers e.g. verapamil, etc.

Others: Digitalis e.g. digoxin, atropine

4.6. Anti-hyperlipidemics

Anti-hyperlipidemics are used to lower high levels of cholesterol that can lead to blood vessel blockade and cause coronary heart disease (CHD). Cholesterol is a lipid normally present in the body that is essential for healthy cell function. Cholesterol levels are measured as total cholesterol, LDL (low density lipoprotein), and HDL (high density lipoprotein). Excess amounts of LDL can lead to blocked blood vessels and cardiovascular problems.

Statins

- Potent competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase)
 - the rate-limiting enzyme in cholesterol biosynthesis
- Are the most effective drugs for lowering LDL

- Cause small increases in HDL
- Drugs include: Lovastatin, simvastatin, atorvastatin, pravastatin and rosuvastatin
- Adverse effects: muscle pain, rash, headache, hepatotoxicity
- Contraindicated in pregnant & lactating women

Practice exercise: for questions 1-10 below, choose most appropriate drug/s from the below listed drugs. Note: one question may have more than one answer.

- | | | |
|-------------------|------------------------|-----------------|
| a. Enalapril | f. Hydrochlorothiazide | k. Hydralazine |
| b. Propranolol | g. Spironolactone | l. Atorvastatin |
| c. Nifedipine | h. Simvastatin | m. Atenolol |
| d. Nitroglycerine | i. Amiodarone | |
| e. Furosemide | j. Digoxin | |

1. It is a class three antiarrhythmic drug. _____
2. A potassium saving/sparing diuretic agent. _____
3. Calcium channel blocker drug used for angina pectoris. _____
4. Anti-angina drug usually given sublingually. _____
5. Antihyperlipidemic drug. _____
6. Cardiac glycoside drug used for heart failure. _____
7. A diuretic agent which may cause ototoxicity. _____
8. A Direct vasodilator used for hypertension. _____
9. A beta blocker which can be used for angina and hypertension. _____
10. A thiazide diuretic commonly used for hypertension. _____

5. Drugs acting on blood and blood forming tissues

Dear trainees, at the end of this session, you are expected to be able to:

- + Describe common types of deficiency anemia and medications used for their treatment
- + Describe the mechanism of action, clinical indications and common adverse effects of anticoagulants and antiplatelets

5.1. Introduction

Blood is the body's only fluid tissue, consisting of cells within a liquid matrix. It is composed of plasma (55%) and blood cells (45%). There are three types of blood cells

- Erythrocytes/RBCs
- Leukocytes/WBCs
- Thrombocytes/Platelets

What does blood do?

- Transportation of Oxygen, Nutrients, Hormones and Waste Products throughout the body
- Regulation of body fluid, electrolyte, Acid-Base balance
- Protection: clot formation (platelets) and fight Infections (WBC)

Hematopoiesis

Hematopoiesis, the production of circulating erythrocytes, platelets and leukocytes from undifferentiated stem cells, is a remarkable process that produces over 200 billion new cells per day in the normal person and even greater number of blood cells in people with conditions that causes loss or destruction of blood cells. The hemopoietic machinery resides primarily in the bone marrow.

Production of red blood cells (Erythropoiesis)

The main job of red blood cells, also known as erythrocytes, is to transport hemoglobin, which in turn carries oxygen from the lungs to the tissues. Hemoglobin (Hb) is the red coloring pigment and the O₂ binding protein of RBC. The function of hemoglobin is to carry O₂ and CO₂.

Red blood cells begin development in the bone marrow and mature in the blood.

Requirements for RBC development

- Healthy bone marrow
- Erythropoietin (stimulant of RBC maturation)
- Iron for hemoglobin synthesis
- Vitamin B12
- Folic acid

If any of these is absent anemia occurs.

5.2. Drugs for Anemia

What is Anemia?

Anemia is the decrease in O₂ carrying capacity of blood

- due to not enough RBC's or
- not enough hemoglobin in RBC's

Types of anemia

- **Deficiency anemia:** Caused by deficiency of factors necessary for erythropoiesis such as: iron, vitamin B12, folic acid
- **Hemolytic anemia:** Caused by excessive destruction of red blood cells
- **Aplastic anemia:** Caused by depression of the bone marrow

Iron deficiency anemia (IDA)

Iron deficiency is the most common cause of chronic anemia. Iron is important structural component of Hemoglobin. Hemoglobin reversibly binds oxygen and transports it from the lungs to other tissues. In the absence of adequate iron small erythrocytes with insufficient hemoglobin are formed giving rise to microcytic hypochromic anemia.

The reduced oxygen-carrying capacity of blood results in listlessness, fatigue, and pallor of the skin and mucous membranes. If tissue oxygenation is severely compromised, tachycardia, dyspnea, and angina may result.

Causes of IDA

- Usually increased demand
 - during periods of accelerated growth in children, and in heavily menstruating or pregnant women
- Inadequate iron supply (malnutrition, malabsorption)
- Chronic blood loss the most common cause of iron deficiency in adults
 - Chronic nose bleeding
 - Menorrhagia
 - Ulcers e.g. PUD.

Treatment of IDA

- Is focused on replenishing iron store
- consists of administration of:
 - Oral iron preparations like ferrous sulfate, ferrous gluconate and ferrous fumarate
 - Parenteral iron preparation like Iron dextran
 - may result in very severe allergic reactions
 - Should be reserved for patient unable to tolerate or absorb oral iron.

Preparation	Tablet Size	Elemental Iron per Tablet	Usual Adult Dosage (Tablets per Day)
Ferrous sulfate, hydrated	325 mg	65 mg	3-4
Ferrous sulfate, desiccated	200 mg	65 mg	3-4
Ferrous gluconate	325 mg	36 mg	3-4
Ferrous fumarate	100 mg	33 mg	6-8
	325 mg	106 mg	2-3

Side effects of oral iron preparations: Nausea, vomiting, Epigastric discomfort, Abdominal cramps, Constipation or Diarrhea.

Of note:

- Oral iron preparations may turn stools black. Reassure the patient that this effect is harmless and should not be interpreted as a sign of bleeding.
- Iron poisoning is common in young children. Store tablets in child-proof containers out of the reach of children.

Vitamin B12 deficiency anemia

- Deficiency results in **Megaloblastic anemia** and **injury to the nervous system**
- Daily vitamin B12 requirement is 2-5 mg
- Dietary source of vitamin B12 is microbially derived vitamin B12 in meat (especially liver), eggs, and dairy products

Vitamin B12 deficiency in humans most often results from malabsorption of vitamin B12 due to lack of intrinsic factor (pernicious anemia).

Treatment

- Drugs: Cyanocobalamin & Hydroxocobalamin.
- For intrinsic factor deficiency the vitamin should be given parenterally (im or Sc) &
- Pts with pernicious anemia will need life-long therapy

Folic acid deficiency

- Deficiency causes megaloblastic anemia and neural tube defects (spina bifida) in developing fetuses.
- Dietary sources: fresh green vegetables, liver, eggs, yeast, and some fruits
- Causes of folic acid deficiency
 - Poor diet
 - Increased demand: Pregnant women have increased folate requirements
- Treatment
 - Folic acid 1mg orally per day

- Folic acid supplements to prevent folic acid deficiency should be considered in high-risk individuals including
 - Pregnant women
 - Patients with hemolytic anemia

Erythropeitin deficiency

- Most common cause is chronic renal failure
- Drugs available for treatment: Epoetin alfa and Darbepoetin alfa
- Epoetin alfa is approved for treating anemia caused by therapy with zidovudine (AZT) in patients with AIDS

5.3. Coagulants and Anti-coagulants

Hemostasis-Is the physiologic process by which bleeding from damaged blood vessel is stopped. clotting is an essential function of blood that prevents excessive blood loss from injuries. Though clotting factors are the primary influence on clotting, adequate platelets and healthy blood vessel walls are also important. Though clotting is primarily intended to prevent blood loss, too much clotting can be dangerous. If a clot (thrombus) is formed in the bloodstream, it can be carried to a location where it blocks a blood vessel and blood flow. Such blockades are called embolisms, and they can cause strokes and death.

Coagulants

- Coagulants are substances that are capable of converting blood from liquid to solid and promote coagulation.
- Coagulant agents
 - Natural vitamin K (phytonadione) may be given orally or by injection
 - A synthetic preparation, menadiol sodium phosphate, is also available
- Clinical use of vitamin K
 - Treatment and/or prevention of bleeding:
 - From excessive oral anticoagulation (e.g. by warfarin)
 - In babies: to prevent haemorrhagic disease of the newborn

Anticoagulants

- Prevent formation of new clots and extension of clots already present
- Anticoagulants are useful in therapy and prophylaxis of venous thromboembolism
 - Used widely in the prevention and treatment of deep-vein thrombosis in the legs,
 - Prophylaxis of embolization in rheumatic heart disease and atrial fibrillation
- Two classes based on their route of administration
 - Parenteral anticoagulant- e.g. Heparin
 - Oral anticoagulant-e.g. warfarin

Heparin

- Heparin cannot be absorbed if given orally, and therefore must be given by injection (IV or Sc).
- Is a preferred anticoagulant for use during pregnancy and in situations that require rapid onset of anticoagulant effects
- adverse effect: Hemorrhage
 - Protamine sulfate is used for treatment of heparin overdose

Warfarin

- Anticoagulant effects occur 3-5 days after oral use
 - Inappropriate for emergencies

Therapeutic uses

- Long-term prophylaxis of thrombosis

Adverse effects

- Spontaneous hemorrhage
- vitamin K (phytonadione) and fresh blood is administered for treatment of warfarin over dosage
- warfarin is contra-indicated in pregnancy

5.4. Anti-platelets

- Suppress platelet aggregation

- Anti-platelets include: aspirin, clopidogrel, ticlopidine
- Used for prophylaxis of arterial thrombosis and myocardial infarction and stroke

5.5. Thrombolytics

- Are given to remove thrombi that have already formed
- Available drugs: streptokinase, urokinase, alteplase, reteplase, tenecteplase
- Therapeutic uses
 - Acute coronary thrombosis (acute MI)
 - Deep venous thrombosis (DVT)
 - Massive pulmonary emboli

Activity: Revise some of the differences and similarities between heparin and warfarin, and share to your group members.

Practice exercise: write the therapeutic uses of the following drugs

1. Iron dextran
2. Vitamin B12
3. Warfarin
4. Heparin
5. Hydroxocobalamin
6. Aspirin

6. Drugs acting on gastrointestinal drugs

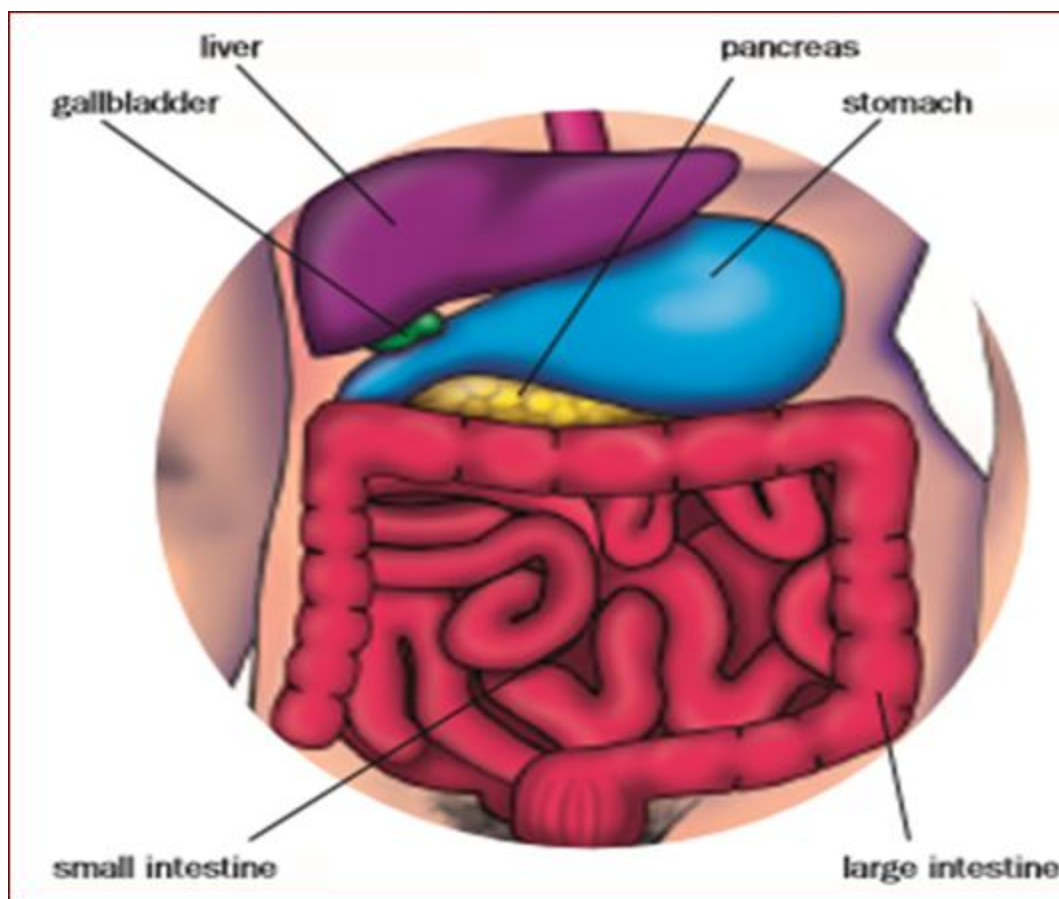
Dear trainees, at the end of this chapter, you will be able to:

-  **List the symptoms and risk factors of GERD and PUD**
-  **List and categorize medications used to treat GERD and PUD**
-  **Describe the mechanism of action and common side effects of antiemetics, laxatives and antidiarrheal drugs**

6.1. Introduction to GIT

The gastrointestinal (GI) tract contains the organs that are involved in the digestion of foods, the absorption of nutrients, and excretion of waste material. These organs include the stomach, gallbladder, liver, pancreas, small intestine, and the large intestine (colon).

Several organs contribute to the digestion of foods by secreting enzymes into the small intestine when food is present. Ducts carry bile from the liver (hepatic duct) and the gallbladder (cystic duct) to the duodenum. The pancreas is located behind the stomach and also contributes enzymes to the digestive process.



The stomach

The stomach, the most distensible part of the GI tract, is located in the upper left abdominal quadrant, immediately below the diaphragm.

Gastric wall consists of; Mucosa, submucosa, muscularis propria, and serosa

Mucosa has two compartments:

- superficial foveolar (meaning leaflike) compartment and deeper glandular compartment

Glandular compartment

- Cardia glands contain mucus secreting cells only
- Oxyntic (fundic) glands contain parietal cells, chief cells and endocrine cells

Parietal Cells

- Produce and secrete gastric acid (HCl)

- Primary site of action for many acid-controller drugs

Chief Cells

- Secrete pepsinogen, a proenzyme
- Pepsinogen becomes pepsin when activated by exposure to acid
- Pepsin breaks down proteins (proteolytic)

Mucoid Cells

- Mucus-secreting cells (surface epithelial cells)
- Provide a protective mucous coat
- Protects against self-digestion by HCl

Gastric acid secretion

- Is a complex, continuous process in which multiple central and peripheral factors contribute to a common endpoint: the secretion of H^+ by parietal cells.
- Acetylcholine (ACh), histamine, and gastrin regulate acid secretion

6.2. Common Gastro-intestinal tract diseases

Gastritis

- A stomach mucosal irritation and inflammation that can be linked to stress, medications, infection, autoimmune disease, alcohol, bile reflux, Helicobacter pylori infection, or NSAID use
- Is characterized by belching, nausea, vomiting, bloating, and a burning sensation

Gastroenteritis:

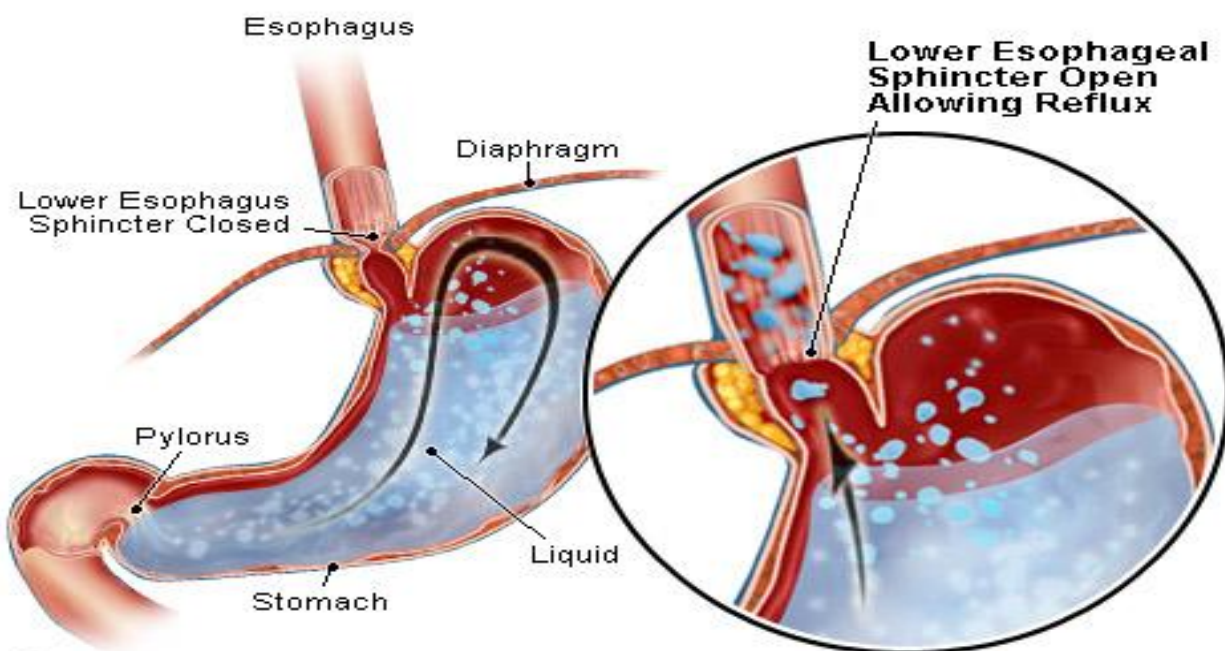
- An inflammation of the lining of the intestines caused by a virus, bacteria, or parasite
- symptoms of diarrhea, abdominal pain, vomiting, headache, fever, chills, and loss of appetite

Gastroesophageal reflux disease (GERD):

- Occurs when acid and pepsin from the stomach flows backward up into the esophagus
- Characterized by radiating burning or chest pain and the presence of an acid taste
- It is often called heartburn.

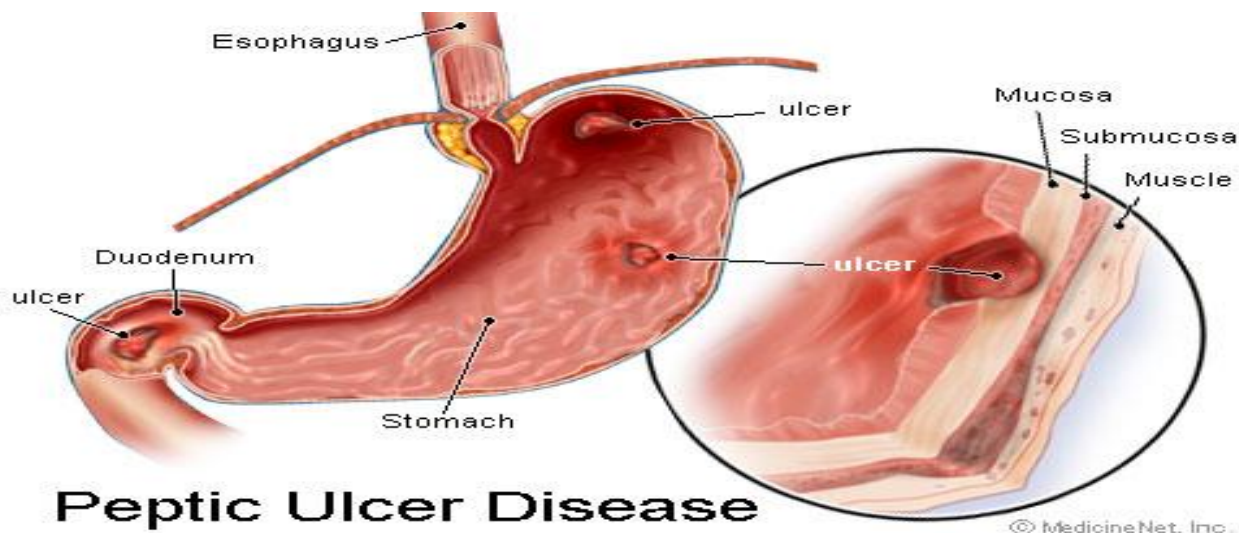
Ulcers (peptic ulcer disease)

- Disorders of the upper GI tract caused by excessive acid secretion.
- Ulcers may be categorized as
 - Gastric ulcers, which are local excavations of the gastric mucosa
 - Duodenal ulcers occur in the duodenum of the intestine and are usually caused by hypersecretion of acid.
 - Stress ulcers develop from the breakdown of the natural mucosal resistance from severe physiologic stress caused by an illness.



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Gastroesophageal Reflux



PUD occurs when there is an imbalance between mucosal defensive factors and aggressive factors. The major protective (defensive) factors are mucus, bicarbonate and prostaglandins. The major aggressive (destructive) factors are *H. pylori*, non-steroidal anti-inflammatory drugs (NSAIDs like aspirin), gastric acid, and pepsin.

There are four major classes of drugs used for acid-peptic diseases including:

- Antacids
- Proton pump inhibitors
- Histamine H₂-receptor antagonists
- Gastric protectants (e.g. Misoprostol and sucralfate)

6.3. Antacids

The principal target of this class of drugs is the neutralization of the acid secreted by parietal cells, thereby lowering the acidity in the stomach.

Commonly used antacids include **Magnesium Hydroxide, Aluminium Hydroxide, Magnesium Trisilicate.**

Magnesium hydroxide

- May produce osmotic diarrhea

- Excessive absorption of Mg^{++} in patients with renal failure may result in toxicity.

Aluminum hydroxide

- Its use is associated with relaxation of gastric smooth muscle, producing delayed gastric emptying and constipation

Side Effects:

Al & Mg are often combined because formulations containing Al alone cause constipation, and formulations containing Mg alone can cause an osmotic diarrhea.

Drug interactions:

Antacids may reduce the absorption of other medications by binding the drug, or by altering a drug's pH-dependent solubility (e.g. tetracyclines, fluoroquinolone, itraconazole, iron).

Antacids neutralize HCL to form salt and water	
Generally, large doses are need (e.g. 7Xdaily)	
Antacids are basic compounds composed of a metal ion and a base	Metal ion; Al^{3+} , Mg^{2+} , Ca^{2+} , Na^{1+}
	Bases; hydroxide, carbonate, bicarbonate, citrate, trisilicate
Therapeutic uses of antacids	Gastric ulcer and duodenal
	Gastroesophageal reflux disease
	Prophylaxis of stress ulceration
	Gastritis

6.4. Proton pump inhibitors (PPI)

- Drugs in this group include omeprazole, pantoprazole, lansoprazole, Esomeprazole
- These drugs ideally should be given about 1hour before meals for improved bioavailability.
- Clinical indication
 - Principally to promote healing of gastric and duodenal ulcers and to treat gastroesophageal reflux disease (GERD)
 - Treatment of hypersecretory conditions (e.g. Zollinger-Ellison syndrome)
 - Reduce the risk of duodenal ulcer recurrence associated with H. pylori infections.
- Most common adverse effects: nausea, abdominal pain, diarrhea, flatulence, and constipation.

Drug	pK _a	Bioavailability (%)	t _{1/2} (h)	T _{max} (h)	Usual Dosage
Omeprazole	4	40–65	0.5–1.5	1–3.5	20–40 mg qd
Esomeprazole	4	> 80	1.2–1.5	1.6	20–40 mg qd
Lansoprazole	4	> 80	1.5	1.7	30 mg qd
Pantoprazole	3.9	77	1.0–1.9	2.5–4.0	40 mg qd
Rabeprazole	5	52	1.0–2.0	2.0–5.0	20 mg qd

6.5. Histamine H₂-Receptor antagonists

- Drugs: Cimetidine, Famotidine, Ranitidine, Nizatidine
- Side effects:
 - H₂ blockers are extremely safe drugs, with side effects in less than 3% of patients (headaches, diarrhea, fatigue).
 - Galactorrhea in women and gynecomastia, reduced sperm count, and impotence in men (with larger dose and/or prolonged use of cimetidine)
- Drug interaction
 - Cimetidine inhibits multiple forms of cytochrome P450
 - May prolonged the half-lives of drugs like warfarin, theophylline, phenytoin, lidocaine, quinidine, propranolol, metoprolol, tricyclic antidepressants, benzodiazepines, calcium channel blockers, sulfonyleureas, and ethanol

Drug	Relative Potency	Dose to Achieve > 50% Acid Inhibition for 10 Hours	Usual Dose for Acute Duodenal or Gastric Ulcer	Usual Dose for Gastroesophageal Re Disease
Cimetidine	1	400–800 mg	800 mg HS or 400 mg bid	800 mg bid
Ranitidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid
Nizatidine	4–10	150 mg	300 mg HS or 150 mg bid	150 mg bid
Famotidine	20–50	20 mg	40 mg HS or 20 mg bid	20 mg bid

6.6. Mucosal protective agents

Also known as cytoprotective compounds. These agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

Drugs in this group include:

- Sucralfate,
- Bismuth subsalicylate and
- Misoprostol
 - Misoprostol has both anti-secretory and mucosal protective effects
 - It is used for prevention of NSAID – induced ulcer

6.7. Eradication of H-pylori

- H. pylori are a gram-negative rod that causes gastritis and is a contributor to peptic ulcer disease, gastric lymphoma.
- The great majority of patients (70-90%) with gastric and duodenal ulcers have H. pylori

- Eradication of *H. pylori* correlates with a reduction in the recurrence of ulcers.
- A combination of antimicrobial drugs and drugs which reduce HCl secretion are used
 - **Omeprazole 20 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 14 days**
 - Metronidazole can also be substituted for amoxicillin in penicillin-allergic patients.

6.8. Emetics and Anti-emetics

Anti-emetics are drugs used to prevent or treat nausea and vomiting. Nausea is an unpleasant sensation of abdominal discomfort accompanied by a desire to vomit. Vomiting is the expulsion of stomach contents through the mouth. Nausea may occur without vomiting and vomiting may occur without prior nausea, but the two symptoms most often occur together

Causes of nausea and vomiting

- Motion sickness
- Pregnancy (morning sickness)
- Drug induced (opioids, anticancer, estrogen preparations)

Emesis not only affects the quality of life but can lead to rejection of potentially curative antineoplastic treatment. In addition, uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

Drugs used in nausea and vomiting belong to several different therapeutic classifications

- Antihistamines
- Anticholinergics
- Dopamine D2 antagonists
- 5-HT₃ (serotonin) Receptor Antagonists

Antihistamines

- Drugs: Promethazine, dimenhydrinate and diphenhydramine
- Primarily useful for motion sickness and postoperative emesis

- Promethazine can be used for severe morning sickness of pregnancy (if absolutely essential)
- Sedation will frequently occur with their administration

Anticholinergics

- Drugs: scopolamine (hyoscine)
- Used as transdermal patch for motion sickness
- Use of antihistamine and anticholinergic drugs is limited by
 - sedation, dizziness, confusion, dry mouth

Dopamine antagonists

- Metoclopramide, chlorpromazine
- Are effective in prevention or treating nausea and vomiting induced by drugs, radiation therapy, surgery and most other stimuli (e.g. pregnancy)
- Are generally ineffective in motion sickness.

5-HT₃ Receptor Antagonists

- Drugs: Ondansetron, Granisetron
- Are the most widely used drugs for chemotherapy-induced emesis
- Also used to prevent or treat post-operative nausea and vomiting
- Headache, dizziness, and constipation (most frequently reported adverse effect)

Emetics

- Are drugs that are used to induce vomiting(emesis)
- Induced emesis is the preferred means of emptying the stomach in awake patients who have:
 - Ingested a toxic substance or
 - Recently taken a drug overdose.
- The most commonly used emetics is syrup of ipecac(emetine)
- Ipecac syrup induces vomiting by direct irritation of the gastric mucosa and it also acts on CTZ (chemoreceptor trigger zone).

6.9. Drugs used for constipation (laxatives)

What is constipation?

- Decreased frequency, difficulty in initiation or passage, passage of firm or small-volume feces, or a feeling of incomplete evacuation

What causes constipation?

- Lack of dietary fiber, drugs, hormonal disturbances, neurogenic disorders, and systemic illnesses.
- In most cases no specific cause is found.

Laxatives are used to increase stool frequency and reduce stool viscosity and thereby used for

- Constipation
- Are also used before radiological, endoscopic, and abdominal surgical procedures
 - such preparations quickly empty the colon of fecal material
- Commonly used laxatives include Magnesium Sulfate, Bisacodyl, cascara sagrada, glycerin, liquid paraffin, docusate sodium, lactulose, senna

6.10. Antidiarrheal agents

Diarrhea involves increase in the motility of the gastrointestinal tract, increased secretion, and a decrease in the absorption of fluid, a loss of electrolytes (particularly Na^+) and water. Severe diarrhea may result in dehydration and electrolyte imbalances.

In many instances, drug intervention is not required because it is a protective mechanism used in an attempt by the body to flush out the offending pathogen or agent.

There are three approaches to the treatment of severe acute diarrhea:

- Maintenance of fluid and electrolyte balance by oral rehydration is the first priority
 - Oral rehydration salt (ORS)

- Use of specific anti-infective agents may be necessary in some types of enteritis (e.g. typhoid, amoebic dysentery and cholera)
- Use of non-antimicrobial antidiarrheal agents for symptomatic treatment of mild or uncomplicated diarrhea
 - Antimotility agents like diphenoxylate and loperamide
 - Adsorbents like kaolin, pectin
 - Agents that modify fluid and electrolyte transport like Bismuth subsalicylate
 - Zinc Sulphate
 - supplementation in zinc-losing conditions

6.11. Anti-flatulent agents: e.g. Simethicone

- **Indications:** Flatulence, gastric bloating, postoperative gas pains
- **MOA:** Reduce surface tension, resulting in gas bubbles being released more easily
- **Adverse reaction:** Diarrhea, nausea

Practice exercise: Choose the best answer for the below questions

1. All are histamine H₂-receptor antagonists **except**
 - a. Cimetidine
 - b. Ranitidine
 - c. Omeprazole
 - d. Famotidine
2. The most effective antiemetic for controlling anticancer induced vomiting is:
 - a. Chlorpromazine
 - b. Ondansetron
 - c. Metoclopramide
 - d. Promethazine
3. Example of "protective factors" in peptic ulcer disease:
 - a. gastric mucus
 - b. Pepsins
 - C. Helicobacter pylori
 - d. NSAIDs
4. Antacid that causes constipation
 - a. aluminum hydroxide
 - b. magnesium hydroxide
5. Which of the following provides mucosal protection in acid peptic disease
 - a. Misoprostol
 - b. Bismuth subsalicylate
 - c. Sucralfate
 - d. All of the above
6. What bacteria contribute to peptic ulcer disease?
 - a. Streptococcus
 - b. Helicobacter pylori
 - c. Helicobacter spirella
7. The drugs employed for eradication of H pylori include the following **except**
 - a. Amoxicillin
 - b. Metronidazole
 - c. Clarithromycin
 - d. Ciprofloxacin
8. Antiulcer drug that may cause gynecomastia and impotence
 - A. Omeprazole
 - B. Amoxicillin
 - C. Cimetidine
 - D. Misoprostol
9. All of the following drugs are proton pump inhibitors **except**:
 - a. Pantoprazole
 - b. Omeprazole
 - c. Ketoconazole
 - d. Rabeprazole
10. Indicate the laxative drug belonging to osmotic laxatives:
 - a. Docusate sodium
 - b. Bisacodyl
 - c. Methylcellulose
 - d. Sodium phosphate

7. Drugs acting on central nervous system (CNS)

Dear trainees, upon completion of this chapter, you will be able to:

- + List neurotransmitters important to the central nervous system
- + Discuss common central nervous system disorders
- + Describe central nervous system drug groups and provide specific examples
- + Describe indications, contraindications and adverse effects commonly prescribed central nervous system drugs

7.1. Introduction

The Central nervous system (CNS) is anatomically divided into: brain and spinal cord. The functional unit of nervous system is called neuron. The structural and functional properties of neurons and their specific receptors provides a means to modify CNS function by administering drugs that can act at defined receptor sites, either causing inhibition or excitation at the receptor.

The brain and spinal cord are protected by bony structures, membranes, and fluid.

The brain is formed of 3 main parts:

- a. **The forebrain:** the cerebrum, the thalamus, the hypothalamus
- b. **The midbrain**
- c. **The hindbrain:** the cerebellum, the pons, the medulla oblongata

The outermost layer of the cerebrum is the cortex. The midbrain, pons and medulla oblongata make the brainstem. The nerves involved are cranial nerves and spinal nerves.

Neurotransmission is essential for the process of communication between nerve cells (neurons). Neurotransmission is the fundamental process that drives information transfer between neurons and their targets. Neurotransmission occurs at specialized regions between neurons and their targets, called the synapse. Neurotransmitters are the chemicals which allow the transmission of signals from one neuron to the next across synapses.

Important transmitters:

Acetylcholine (ACh): is thought to play a major role in cognitive functions and memory formation as well as motor control. It acts on muscarinic and nicotinic receptors. Drugs that decrease ACh are used to treat Parkinson's disease. Drugs that increase ACh are used to enhance memory.

Dopamine: controls behavior, motor control, hormone release, and emesis. Areas of the brain where dopaminergic receptors have been found are limbic system and extrapyramidal system. Dopamine acts on D1 and D2 receptors. Drugs that decrease dopamine are used to treat schizophrenia. Drugs that increase dopamine are used to treat Parkinson's disease.

Noradrenaline and Serotonin (5-HT): involved in arousal, sleep, mood, appetite, and temperature control and hormone release. Noradrenalin acts on α and β receptors. 5-HT acts on 5-HT1 and 5-HT2. Drugs that increase noradrenaline and serotonin are used to treat depression. Drugs that decrease serotonin are used to treat schizophrenia.

GABA: is a major inhibitory neurotransmitter distributed throughout the brain and the spinal cord. It inhibits motor control, arousal, memory formation and consciousness. It acts on GABA_A and GABA_B receptors. Drugs that enhance the action of GABA are used to treat anxiety, insomnia and epilepsy.

Enkephalin, Dynorphin, Endorphin: natural opioids that decrease pain.

Definitions of important terms

Addiction: a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.

Analgesics: medicines that are used to relieve pain (provide analgesia).

Anesthesia: a way to control pain during a surgery or procedure by using medicine called anesthetics.

Anxiety: a feeling of worry, nervousness, or unease about something with an uncertain outcome.

Chemical synapses: are biological junctions through which signals from neurons can be exchanged to each other and to non-neuronal cells such as those in muscles or glands.

Dependence: is an adaptive state that develops from repeated drug administration, and which results in withdrawal upon cessation of drug use.

The limbic system: a group of cortical and subcortical structures involved in memory formation and emotional responses. The major parts of limbic system are the hypothalamus, the basal ganglia, and the hippocampus

Narcotic: an addictive drug affecting mood or behavior.

Neuron or nerve cell: is an electrically excitable cell that receives, processes, and transmits information through electrical and chemical signals. A typical neuron consists of a cell body (soma), dendrites, and an axon

Opioids: are substances that act on opioid receptors to produce morphine-like effects. Medically they are primarily used for pain relief, including anesthesia.

Pain: is an unpleasant sensory and emotional experience associated with actual or potential tissue damage

Psychotropic: drugs that affect a person's mental state.

Tolerance: reduced reaction to a drug following its repeated use.

Extrapyramidal system: is involved in the regulation of gross voluntary movements, thus it complements the function of the pyramidal system. The “basal ganglia” constitute an essential part of this system.

The pyramidal system: originates from the motor area of the cerebral cortex and passes through the spinal cord, therefore it is also known as the “corticospinal tract”. It is responsible for the regulation of the fine voluntary movements.

Bipolar disorder (manic-depressive illness): a brain disorder that causes unusual shifts in mood between depression and mania.

Mania: excitement manifested by mental and physical hyperactivity, disorganization of behavior, and elevation of mood

Drugs acting on CNS were among the first to be discovered by primitive humans and are still the most widely used group of pharmacologic agents. In addition to their use in therapy, many drugs acting on the CNS are used without prescription to increase the sense of well-being. The mechanisms by which various drugs act in the CNS have not always been clearly understood. Generally, most drugs act on specific receptors that modulate synaptic transmission.

Drugs that act on CNS include sedative-hypnotics (anxiolytics), antidepressants, mood stabilizers, antipsychotics, anti-seizures, anesthetics, muscle relaxants, analgesics and antiparkinsonian agents.

7.2. Sedatives-hypnotics (Anxiolytics)

- Often these drugs are referred to as sleeping pills. Their effects range from calming down anxious people to promoting sleep.
- The most important drug classes are benzodiazepines and barbiturates.

A. **Benzodiazepines:** chlordiazepoxide, diazepam, alprazolam, lorazepam

- Benzodiazepines are a class of drugs primarily used for treating anxiety and insomnia, but they also are effective in treating several other conditions such as epilepsy and muscle disorder. They are also as part of anesthesia due to their amnesiac properties.
- Benzodiazepines enhance the activity of GABA, effectively slowing nerve impulses throughout the body. This neurotransmitter has an inhibitory effect on motor neurons, thus the presence of GABA slows or stops neuronal activity.
- Due to their sedative properties, benzodiazepines have a high potential for abuse, especially when used with other depressants such as alcohol or opiates.
- **Common side effects include:** Lightheadedness, Drowsiness, Confusion, Sedation, Memory impairment, Tolerance, Dependence

B. **Barbiturates: Thiopental, Phenobarbitone**

- ✚ The effects of barbiturates are, in many ways, similar to the effects of alcohol.
- ✚ Small amounts produce calmness and relax muscles. Larger doses can cause slurred speech, memory loss, and irritability (bad temper/impatience), changes in alertness, decreased interpersonal functioning, staggering gait, poor judgment, and slow, uncertain reflexes. These effects make it dangerous to drive a car or operate machinery.
- ✚ Large doses can cause unconsciousness and death.
- ✚ Barbiturates may also pass through the placenta, creating birth defects and behavioral problems in babies.
- ✚ They cause dependence

7.3. Antidepressants

- + **Depression:** a mood disorder that causes a persistent feeling of sadness and loss of interest.
- + Antidepressants are a broad group of drugs that are used in the treatment of depression. Although they do not cure depression, they are usually effective at improving mood and relieving symptoms such as restlessness, anxiety, sleep problems, and suicidal thoughts.
- + Antidepressants are also sometimes used to treat people with long-term (chronic) pain.
- + A **decrease** in the level of norepinephrine, 5-HT (serotonin) and dopamine causes depression. Antidepressants relieve depression by **increasing** the level of norepinephrine, serotonin and dopamine.

The following are commonly used antidepressant classes:

1. **Tricyclic antidepressants (TCA):** imipramine, amitriptyline
2. **Selective serotonin reuptake inhibitors (SSRI):** fluoxetine, sertraline, citalopram.

Adverse effects

- ✓ In general, the most common side effects of antidepressants are usually mild. Side effects should improve within a few days or weeks of treatment, as the body gets used to the medication.
- ✓ Side effects like loss of sexual desire, erectile dysfunction and decreased orgasm may last longer
- ✓ Common side effects of antidepressants include:

Both TCA and SSRI side effects

- ✓ Dizziness
- ✓ Nausea
- ✓ Increased appetite and weight gain
- ✓ **Sexual dysfunction:** loss of sexual desire, erectile dysfunction and decreased orgasm

TCA only side effects

- ✓ Anticholinergic side effects (dry mouth, blurred vision, constipation)
- ✓ Hypotension

7.4. Mood Stabilizers

- Lithium carbonate, sodium valproate, carbamazepine, lamotrigine
- Mood stabilizers are medicines that treat and prevent highs (mania) and lows (depression). They help to keep moods from interfering with work, school, or social life.
- **Lithium carbonate:** is the "classic" mood stabilizer, the first to be approved by the US FDA, and still popular in treatment. Therapeutic drug monitoring is required to ensure lithium levels remain in the therapeutic range: 0.6 or 0.8-1.2 mEq/L (or millimolar).
- **Adverse effects:** nausea, vomiting, diarrhea, ataxia, weight gain, blurred vision, tremor. In general, these side-effects occur in the first few weeks after commencing lithium treatment. Lithium can also cause birth defects if taken during pregnancy.

7.5. Antipsychotic Drugs

- Anti-psychotics are drugs used to treat schizophrenia.
- Schizophrenia is characterized by thoughts or experiences that seem out of touch with reality, disorganized speech or behavior and decreased participation in daily activities. Difficulty with concentration and memory may also be present. People with schizophrenia may have difficulty distinguishing between what is real and what is imaginary.
- Symptoms typically come on gradually, begin in young adulthood, and last a long time.
- Common symptoms include false beliefs (delusion), unclear or confused thinking, hearing voices that others do not hear (hallucination), reduced social engagement and emotional expression, and a lack of motivation
- The exact cause of schizophrenia is not known, but a combination of genetics and drug abuse may play a role.
- The "dopamine theory of schizophrenia" states that schizophrenia is caused by an overactive dopamine system in the brain. There is another theory, "serotonin theory", which states that schizophrenia is caused by overactive serotonin. The two theories are compatible. Thus, drugs used to treat schizophrenia act, by reducing the activity of either dopamine or serotonin.
- The mainstay of treatment is antipsychotic medication, along with counseling, job training and social rehabilitation.

- Antipsychotics, also known as neuroleptics or major tranquilizers, are a class of medication primarily used to manage psychosis, principally in schizophrenia and bipolar disorder. Antipsychotics are classified into two:

1. Typical Antipsychotics (neuroleptics or 1st generation antipsychotics)

- Act by inhibiting the activity of the neurotransmitter dopamine
- Examples: Chlorpromazine, Thioridazine, Fluphenazine, Haloperidol
- Possible Adverse reactions of 1st generation anti-psychotic drugs include:
 - A. Extrapyramidal side-effects
 - a. Parkinson's disease-like symptoms - tremor, muscle rigidity, loss of facial expression
 - b. Dystonia - contraction of muscles
 - c. Akathisia: -Restlessness
 - d. Tardive dyskinesia - involuntary, abnormal movements of the face, mouth, and/or body. This includes lip smacking and chewing movements.
 - B. anticholinergic side effects (blurred vision, dryness of mouth, constipation, urinary retention and tachycardia)
 - C. Sedation, orthostatic hypotension, weight gain
 - D. Neuroleptic malignant syndrome: rare but a serious.

- 2. Atypical antipsychotics** (2nd generation antipsychotics): clozapine, olanzapine, risperidone,
- Act by inhibiting the neurotransmitters serotonin and dopamine

Atypical antipsychotics are less likely to produce extrapyramidal side effects (such as tremor and Parkinson's-like symptoms) and tardive dyskinesia (abnormal, repetitive facial movements). Atypical antipsychotics are also more likely to improve cognitive function.

Adverse effects include: hyperglycemia, weight gain, hyperlipidemia, sexual and cardiac dysfunction. Clozapine can cause agranulocytosis.

7.6. Anti-Parkinson's drugs

Parkinson Disease: characterized tremor, rigidity and difficulty in the coordination of fine muscle movements. The other important feature is Bradykinesia/hypokinesia.

The main problem is in the basal ganglia portion of the midbrain.

- Loss of Dopamine
- High activity of Acetylcholine

Treatment strategies:

1. Decreasing the Muscarinic Activity: help to control tremors and rigidity though they are not of much help in hypokinesia.
e.g. Benztropine, Trihexyphenidyl
2. Increasing the dopaminergic activity: help control bradykinesia
e.g. Sinemet (Levodopa + carbidopa), Bromocriptine

7.7. Anti-seizure drugs

A seizure happens when abnormal patterns of electrical activity arise in the brain. It may cause the body to move in an uncontrolled way, and can also cause loss of consciousness for a short period. Seizures are also known as convulsions when there are uncontrollable muscle contractions. But not all seizures produce convulsive behavior, e.g. Absence seizures involve only brief periods of staring and have no convulsion.

The symptoms produced by a seizure are dependent on which part of the brain is experiencing the abnormal electrical activity. Seizures are generally short-lived – from 15 seconds to 15 minutes – however; there is a life-threatening type of seizure, status epilepticus, in which the seizure continues for longer period of time.

A variety of conditions and substances can trigger seizures. Common causes include congenital abnormalities of the brain, illicit drug use, fever, brain tumors and metabolic imbalances, such as high levels of glucose or sodium.

Epilepsy is a condition in which a person experiences repeated seizure, due to an overall electrical disturbance in the brain. It usually begins in childhood, but can start at any age.

Anti-seizure drugs help control seizures in about 70% of people. They work by increasing the level of GABA and decreasing the levels of sodium and calcium in brain. They don't cure epilepsy, but can stop seizures happening.

The most common anti-seizure drugs include:

- Phenytoin
- Sodium valproate
- Carbamazepine
- Lamotrigine
- Ethosuximide (for absence seizure only)
- Phenobarbitone
- Diazepam

Both seizures and medications are associated with some risks. Seizure control is critical because the risks from seizures are greater than the risks from medications. For example, generalized tonic-clonic seizures are associated with increased risk to both the mother and baby:

- Trauma from falls or burns
- Increased risk of premature labor
- Miscarriages
- Lowering of the baby's heart rate
- Change in seizures
- The most common malformations include cleft lip and cleft palate (which can be surgically corrected), problems with the heart, urinary or genital systems.

Common adverse effects of anti-seizure drugs include:

- Drowsiness, A lack of energy, Blurred vision, headaches, Tremor, Hair loss or unwanted, hair growth, Rashes
- **Phenytoin only side effects**
 - Swollen gums (Gingival hyperplasia)
 - Long-term use may lead to development of peripheral neuropathies and osteoporosis
- **Sodium valproate only side effects**

- Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently

7.8. Anesthetics

- + Anesthesia is defined as “loss of sensation”
- + Medications that cause anesthesia are called anesthetics
- + Anesthetics are used during tests and surgical operations to numb sensation in certain areas of the body or induce sleep. This prevents pain and discomfort, and enables a wide range of medical procedures to be carried out.
- + Anesthetics work by stopping the nerve signals that keep you awake and aware from reaching your brain. During this state of induced sleep, procedures can be carried out without you feeling anything. After the anesthetic has worn off, the nerve signals will be able to reach your brain, and consciousness and feeling will return

Anesthetics are classified into two:

- Local anesthetic:** used during minor procedures where a small area of the body is numbed and you remain fully conscious.
 - Two basic classes of local anesthetics exist
 - Amino amides: lidocaine, bupivacaine
 - Amino esters: procaine, tetracaine
 - Amino esters are much more likely than amino amides to cause allergic hypersensitivity reactions.
- General anesthetic:** used for more serious operations where you're totally unconscious and unaware of the procedure.
 - General anesthetics are classified in to injectable and inhalation type
 - Injectable: propofol, ketamine, Thiopental
 - Inhalation: nitrous oxide, halothane, enflurane

The purpose of general anesthetic is to induce:

- + Analgesia - remove natural response to pain
- + Amnesia - memory loss
- + Immobility - removal of motor reflexes

- + Unconsciousness
- + Skeletal muscle relaxation.

Common adverse effects of general anesthetics include

- Nausea and vomiting
- Shivering and feeling cold
- Confusion and memory loss
- Urinary retention
- Dizziness

7.9. Opioid analgesics

+ **Drugs: Morphine, Codeine, Meperidine (pethidine), Methadone, Tramadol**

+ When you have a mild headache, an over-the-counter pain reliever (e.g. Paracetamol) is usually enough to make you feel better. But if your pain is more severe, stronger analgesics like opioids are needed.

+ Opioids are used to treat moderate to severe pain that may not respond well to other pain medications. Opioids are among the most effective pain medications.

+ Opioids are also used to treat dry cough (antitussive effects)

+ Opioid drugs work by binding to opioid receptors (μ read as mu) in the brain, spinal cord, and other areas of the body. They reduce the sending of pain messages to the brain and reduce feelings of pain.

+ **Common side effects of opioid** include:

- ✓ Sedation
- ✓ Dizziness
- ✓ Nausea and vomiting
- ✓ Constipation
- ✓ Dependence and tolerance
- ✓ Respiratory depression

+ Naloxone is specific antidote for opioid poisoning

7.10.Muscle relaxants

- + The goal with these medications is a reduction of skeletal muscle spasms, muscle spasticity, relief of pain.
- + **Muscle spasms** or cramps are sudden, involuntary contractions of a muscle or group of muscles. They can be caused by too much muscle strain and lead to pain. They're associated with conditions such as lower back pain, neck pain, and fibromyalgia.
- + **Muscle spasticity**, on the other hand, is a continuous muscle spasm that causes stiffness, rigidity, or tightness that can interfere with normal walking, talking, or movement. Muscle spasticity is caused by injury to parts of the brain or spinal cord involved with movement.
- + **Anti-spastics** are used to treat muscle spasticity and include the following
 - Baclofen
 - Dantrolene
 - Diazepam
- + **Anti-spasms** are used to treat muscle spasm and include the following.
 - Chlorzoxazone
 - Methocarbamol
 - Orphenadrine
- + **Neuromuscular blockers** are used in conjunction with an anesthetic to provide skeletal muscle relaxation during surgery
 - D-Tubocurarine, vecuronium, mivacurium
 - Succinylcholine

Practice exercise: Choose the best answer from given alternatives for the following questions.

1. Which of the following drugs is an opioid analgesic?
 - a. Paracetamol b. Naloxone c. Pethidine
2. Which one of the following drugs is a typical antipsychotic drug?
 - a. Chlorpromazine b. clozapine c. Haloperidol d. 'a' and 'c'
3. Antipsychotic drug with least extrapyramidal side effects:

- a. Chlorpromazine
 - b. Haloperidol
 - c. Clozapine
 - d. Carbamazepine
4. A 10-year-old boy who was taking anti-epileptic drug developed an overgrowth of gum tissue (**gingival hyperplasia**). This patient was most likely receiving which of the following agents?
- a. Ethosuximide b. Clonazepam c. Phenobarbitone d. Phenytoin
5. Indicate a tricyclic antidepressant drug
- a. Fluoxetine b. Amitriptyline c. Diazepam
6. Drug of first choice for absence seizures
- a. Phenobarbitone b. Ethosuximide c. Phenytoin d. Carbamazepine
7. Which of the following local anesthetic is more likely to cause allergic reaction
- a. Lidocaine b. Bupivacaine c. Procaine d. Ropivacaine
8. Why are local anesthetics frequently administered in combination with a vasoconstrictor like epinephrine?
- a. To delay systemic absorption of the anesthetic
 - b. To enhance systemic absorption of the anesthetic
 - c. To decrease metabolic degradation of the anesthetic
 - d. To decrease the hypersensitivity reactions of the anesthetic
9. Which of the following is an injectable general anesthetic?
- a. Halothane b. ketamine c. nitrous oxide d. enflurane
10. A benzodiazepine used for treating anxiety and insomnia (lack of sleep)
- a. Phenobarbitone b. diazepam c. thiopental

8. Drugs for Inflammatory Disorders

Dear trainees, at the end of this chapter, you will be able to:

- ✚ Describe the mechanism of action, clinical indications and common adverse effects of antihistamines and NSAIDs
- ✚ List and classify medications used in the treatment of and gout.
- ✚ Describe the mechanism of action for each class of drugs used in the treatment of hyperuricemia and gout

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents.

Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair.

When healing is complete, the inflammatory process usually settles.

However, inappropriate activation of the immune system can result in inflammation, leading to immune mediated diseases.

8.1. Autacoids

“**Autacoids**” is to mean “self-remedy” which are commonly used without prescription. It is collective term for various hormones such as **histamine, prostaglandins, leukotrienes**, and **cytokines**. These are sometimes also called local hormones.

They play important roles in physiologic processes and also have several pharmacological significances.

Histamine: The body effects include

- involved in vascular dilatation and edema formation (increase of excess fluid between tissues)
- bronchospasm (constriction of bronchial tree)
- stimulant of HCl secretion

- awaking our brain
- induction of itching and pain
- Histamine plays very important role in **anaphylaxis** and other forms of **allergic reactions**.
 - **Anaphylaxis** is condition of the body where there is extreme sensitivity to substance occurs

Treatment of Anaphylaxis

- ® Preventing exposure to the offending factors
- ® Treating occasionally with corticosteroids.
- ® Giving adrenaline and correcting hypotension

Prostaglandins:

They play an important role in the development of the inflammatory response in association with other mediators.

The effects on body including bronchodilator action, increase intestinal motility, inhibits gastric acid secretion and protecting the gastroduodenal mucosa cells from acid effect are more often.

Drugs include:

- ® carboprost
- ® Dinoprostone (prostaglandin E2)
- ® misoprostol.

Therapeutic uses include:

- ® cervical ripening and labor induction,
- ® control of postpartum hemorrhage,
- ® induction of abortion (Dinoprostone)
- ® Prophylaxis of NSAID-induced peptic ulcers(misoprostol).

Adverse Effects include: fever, diarrhea, abdominal cramps, headache, nausea, and vomiting.

Homework exercise

1. Explain the antagonistic effects of histamine and adrenaline
2. Discuss the consequences of inhibition of prostaglandin synthesis

8.2. Antihistamines

- These drugs competitively block histamine receptors (H1 receptors) to diminish or abolish the main actions of histamine in the body
- They do not inactivate histamine or prevent its synthesis or release.
- H1 receptors are responsible for vasodilatation, itch reactions in the skin, and to some extent for contractions of smooth muscle in the bronchi and gastro-intestinal tract.
- Divided into first-generation and second-generation agents
 - Second generation agents are less sedating
- First generation: e.g. Chlorpheniramine, Cyproheptadine, Diphenhydramine, dimenhydrinate, chlorpheniramine, Promethazine
- Second generation: e.g. Cetirizine, Loratadine

Anti-histamines are used for treatment of allergic disorders:

- Symptomatic relief of hypersensitivity reactions including urticaria and angioedema, rhinitis, and conjunctivitis, skin disorders such as atopic eczema

Other uses include:

- the symptomatic treatment of coughs and the common cold (often with a decongestant)
 - Prophylaxis of migraine, particularly in children.
 - Treating sleep problem(insomnia)

Side effects: sedation, drowsiness to deep sleep, and including tiredness, dizziness

Caution and Contraindications:

- Antihistamines should not be given to premature infants or neonates; and children under 1 year of age to children under 2 years.

- They should be used with caution in prostatic hypertrophy, urinary retention, and glaucoma (intraocular pressure)
- the patient should be informed to exercise extreme caution when driving or doing other hazardous activities because these drugs cause sedation.

8.3. Non-steroidal anti-inflammatory drugs (NSAIDs)

- ® The NSAIDs are a group of agents that have antipyretic (fever reduction), analgesic (pain reduction) and anti-inflammatory effects
- ® They all inhibit prostaglandin biosynthesis by blocking **cyclooxygenase** enzyme
- ® Cyclo-oxygenase enzyme catalyzes synthesis of prostaglandins from arachidonic acid (see fig. below)
- ® Inhibition of cyclooxygenase-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, while inhibition of cyclooxygenase-1 is responsible for prevention of cardiovascular events and most adverse events

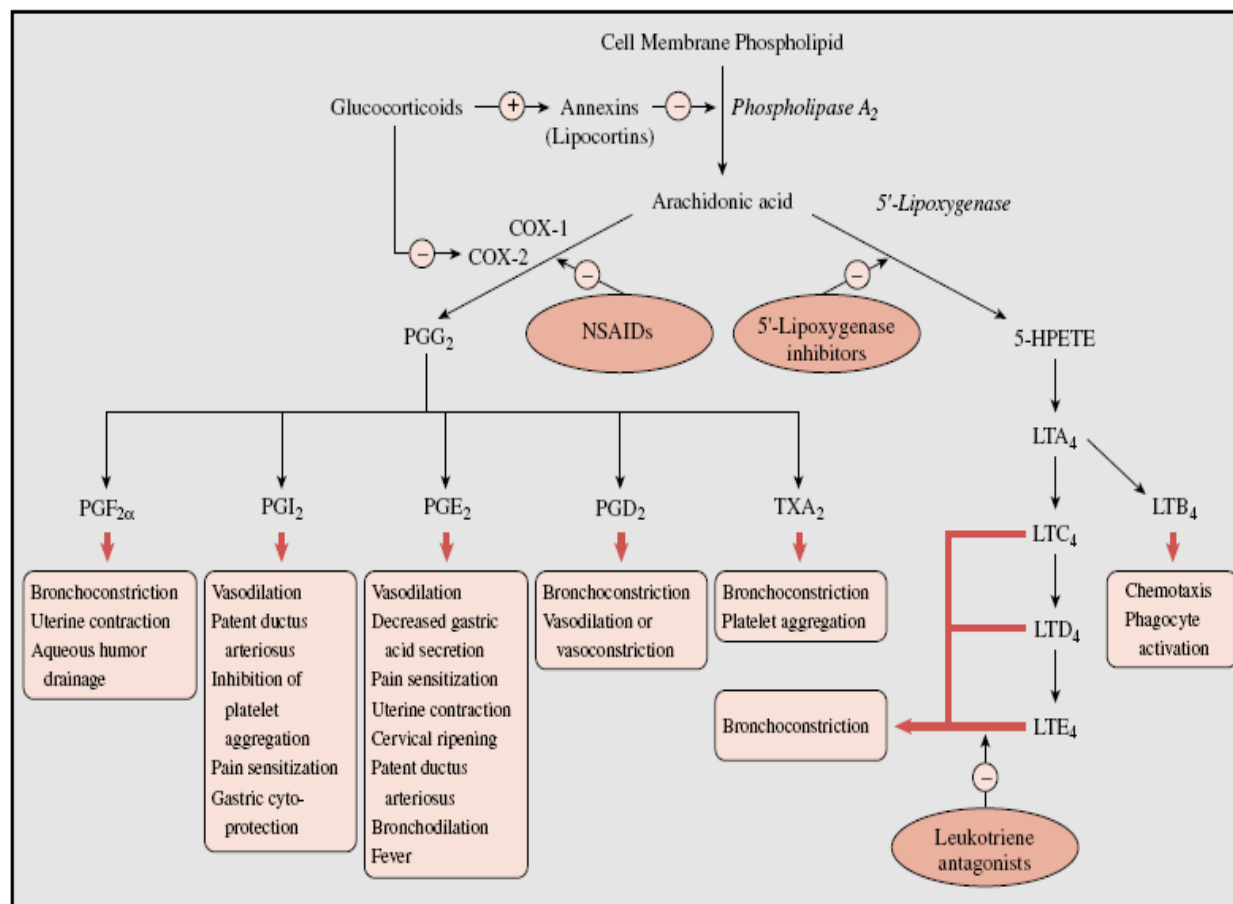


Fig.8.1: Biosynthesis of inflammatory mediators and anti-inflammatory drugs mechanism of action

The drugs include:

- Aspirin, Ibuprofen, Diclofenac, Piroxicam, Indomethacin, Meloxicam, Paracetamol

Therapeutic uses:

- NSAIDs are used in the treatment of osteoarthritis, gout, and rheumatoid arthritis
- To alleviate fever (Aspirin, ibuprofen, and naproxen)
- Reduce the incidence of myocardial infarction (low dose aspirin)
- Used topically to treat acne, corns, calluses, and warts (Salicylic acid;

Adverse effects of NSAIDs

Because of the associated adverse events below, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

- GI related(intolerance), ranging from dyspepsia to bleeding
- Prolonged bleeding time (aspirin anti-platelet effect)
- Urticaria, bronchoconstriction, and angioedema
- Increased risk for myocardial infarction and stroke with all NSAIDs except **aspirin**.
- **Toxicity:** for aspirin (salicylism): nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears)
- Note: **paracetamol** is preferred if analgesic or antipyretic effects are needed during pregnancy.
- NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus

Paracetamol (Acetaminophen)

- inhibits prostaglandin synthesis in the CNS
- it has antipyretic and analgesic properties but no anti-inflammatory
- It does not affect platelet function or increase bleeding time. It is not considered to be an NSAID
- It is a suitable substitute for
 - the analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/risks,
 - in those whom a prolongation of bleeding time is not desirable,
 - as well as those who do not require the anti-inflammatory action of NSAIDs
 - choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin)
- Well tolerated at therapeutic doses
- Overdosage causes a potentially fatal hepatic necrosis

Aspirin

- ✓ Aspirin rapidly absorbed from the stomach and upper small intestine, but the drug may damage the mucosal barrier.
- ✓ Alkalinization of the urine increases the rate of excretion of free aspirin.

- ✓ the main **adverse effect** is gastric upset (intolerance)

Ibuprofen

- Ibuprofen is extensively metabolized in the liver.
- Gastrointestinal irritation and bleeding occur, though less frequently than with aspirin.
- Rash, pruritus, tinnitus, dizziness, headache, and fluid retention have been reported.
- Rare hematologic effects include agranulocytosis and aplastic anemia.
- Effects on the kidney include acute renal failure, interstitial nephritis, and nephrotic syndrome, occurring very rarely.

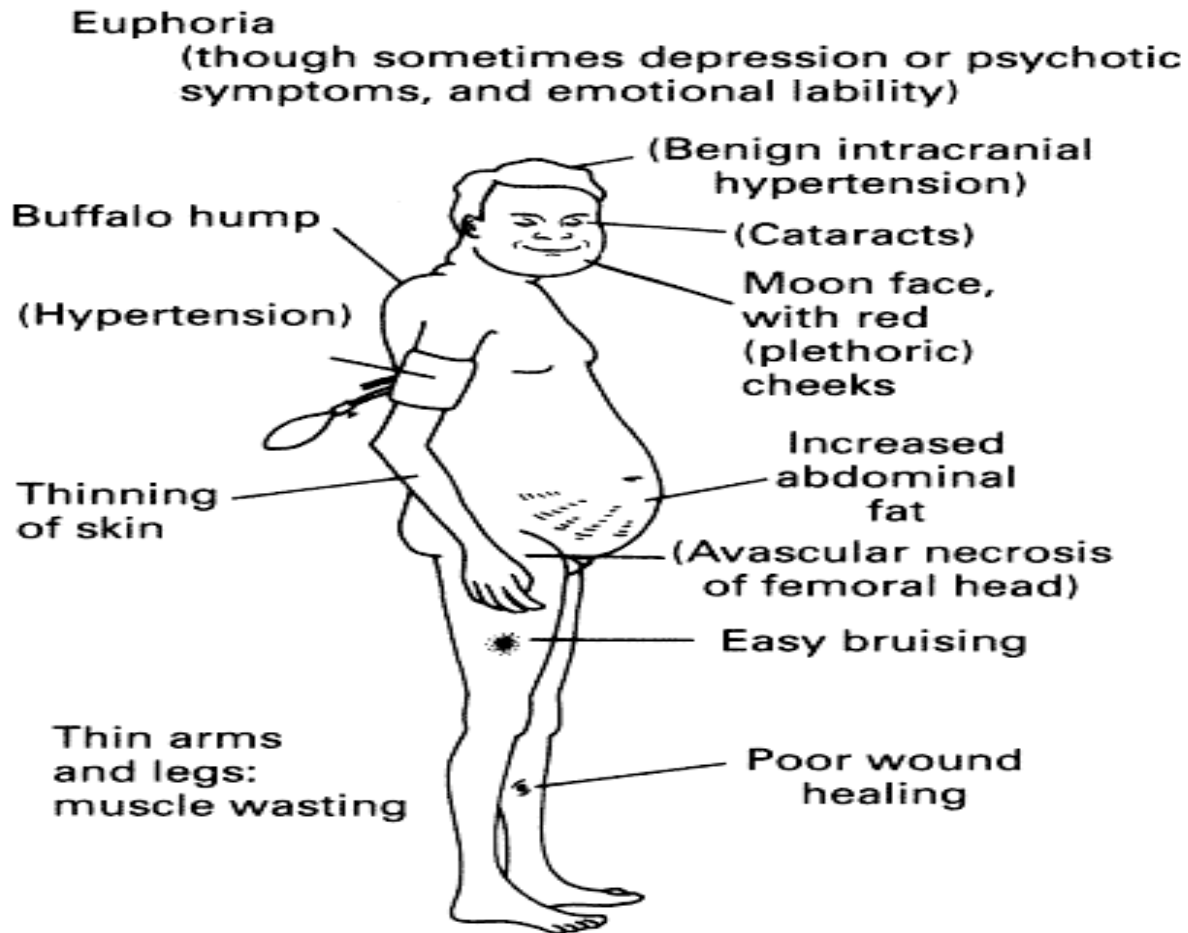
Diclofenac

- The drug is rapidly absorbed following oral administration
- The drug is recommended for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis and for the treatment of acute musculoskeletal pain.
- Adverse effects include gastrointestinal distress, occult gastrointestinal bleeding, and gastric ulceration.

8.4. Steroidal anti-inflammatory drugs

Corticosteroids are used to suppress inflammation, allergy and immune responses. They are useful in many inflammatory conditions like rheumatoid arthritis, eye and skin inflammation, and asthma. Though they are very effective anti-inflammatory agents, they are associated with severe adverse effects, specially when used for systemic action. Thus, they are usually used for local action and if systemic, they should not be used for long time.

Adverse effects of corticosteroids



Also:

Osteoporosis

Tendency to hyperglycaemia

Negative nitrogen balance

Increased appetite

Increased susceptibility to infection

Obesity

Table 8.1: Corticosteroid Preparations

Corticosteroid Preparations	Indications	Dosage form available
Betamethasone	✓ management of non-infected inflammatory conditions of the external ear ✓ inflammatory dermatoses ✓ treatment of primary and secondary skin infections	Tablet, 0.5mg; Injectable suspension, 0.6mg/ml
Dexamethasone	✓ suppression of inflammatory and allergic disorders; ✓ shock; diagnosis of Cushing's disease ✓ nausea and vomiting with chemotherapy; ✓ rheumatic disease;	Tablet ,0.5mg, 0.75mg, 1mg, 2mg, 4mg Injection, 4mg/ml, 25mg/ml, 50mg/ml
Hydrocortisone	✓ adrenocortical insufficiency; ✓ Hypersensitivity reactions including anaphylactic shock inflammatory bowel disease.	Injection (Sodium Succinate), 50mg/ml in 2ml ampoule, 125 mg/ml
Methyl prednisolone Acetate	✓ Rheumatoid Arthritis	Tablet 5mg, 10mg Injection, 40mg/ml, 80mg/ml in 1ml and 2ml ampoules
Prednisolone	✓ treatment of asthma ✓ Rheumatic fever ✓ Pyrogenic (in meningitis) ✓ Immune thrombocytopenic purpura	Tablet, 1mg, 3.5mg, 5mg, 10mg Injection, 10mg/ml, 25mg/ml in 2ml ampoule
Triamcinolone Acetonide	✓ suppression of inflammatory and allergic disorders ✓ rheumatic disease	Tablet 4mg; Injection, 10mg/ml, 40mg/ml in vial;

Frequently seen **adverse** effects of topical steroid therapy:

- ✓ Atrophy of the epidermis, steroid acne
- ✓ Disturbances of wound healing;
- ✓ disturbances of pigmentation,
- ✓ Glaucoma
- ✓ Hyperglucemia
- ✓ Fluid retention and hypertension

8.5. Drugs used in treatment of gout

- Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia) leading to acute arthritis in joints and cartilage
- Gout is usually associated with high serum levels of uric acid, a poorly soluble substance that is the major end product of purine metabolism.
- **The aim of treatment:**
 - relieving the acute gouty attack and preventing recurrent gouty episodes

Treatment of acute gout

- ✓ Colchicine; NSAIDs (Indomethacin); and corticosteroids,

Treatment of chronic gout

- ✓ Allopurinol (Xanthine oxidase inhibitors)
- ✓ Probenecid (Uricosuric agents): increase excretion of uric acid

Colchicine:

- ✓ Is administered orally and is rapidly absorbed from the GI tract.
- ✓ It is recycled in the bile and is excreted unchanged in feces or urine.
- ✓ Adverse effects are:
 - Causes diarrhea and may occasionally cause nausea, vomiting, and abdominal pain.
 - May rarely cause hair loss and bone marrow depression
 - Burning throat pain, bloody diarrhea, shock, hematuria, and oliguria.

Allopurinol

- ✓ Is completely absorbed after oral administration.
- ✓ The drug and its active metabolite are excreted in the feces and urine.
- ✓ The dosage should be reduced if the creatinine clearance is less than 50 mL/min
- ✓ **Adverse effects:** well tolerated by most patients.
 - Hypersensitivity reactions, (skin rashes), in those with reduced renal function

Probenecid

- ✓ is a uricosuric drug
- ✓ promotes renal clearance of uric acid by inhibiting the urate anion exchanger in the proximal tubule that mediates urate reabsorption at therapeutic doses
- ✓ It also inhibits the excretion of penicillin, methotrexate, and some NSAIDs (indomethacin)
- ✓ It should be avoided for the patient with reduced renal function

Practice exercise: Choose the best answer for the following questions

1. The indication of non-steroidal anti-inflammatory (NSAIDs) drug include:

A. Treatment of pain	D. treatment of fever
B. Treatment of Anaphylaxis	E. all of the above
C. rheumatoid arthritis	
2. select the anti histamine drug

A. paracetamol	C. diclofenac
B. ibuprofen	D. Diphenhydramine
3. Gout is treated by

A. Allopurinol	C. Indomethacin
B. Colchicines	D. All of the above

Case study

Mr. RR is 54-year-old male and come with signs and symptoms of an acute gouty flare. His doctor wishes to treat him to improve his symptoms first and also treat him for chronic improvement.

- i. Which of the drug for gout is/are most likely to acutely improve his gout symptoms and pain?
- ii. Which of the drug for gout would be better for chronic improve his gout?
- iii. Do you think that **Mr. RR will be okay with combination of drugs?**

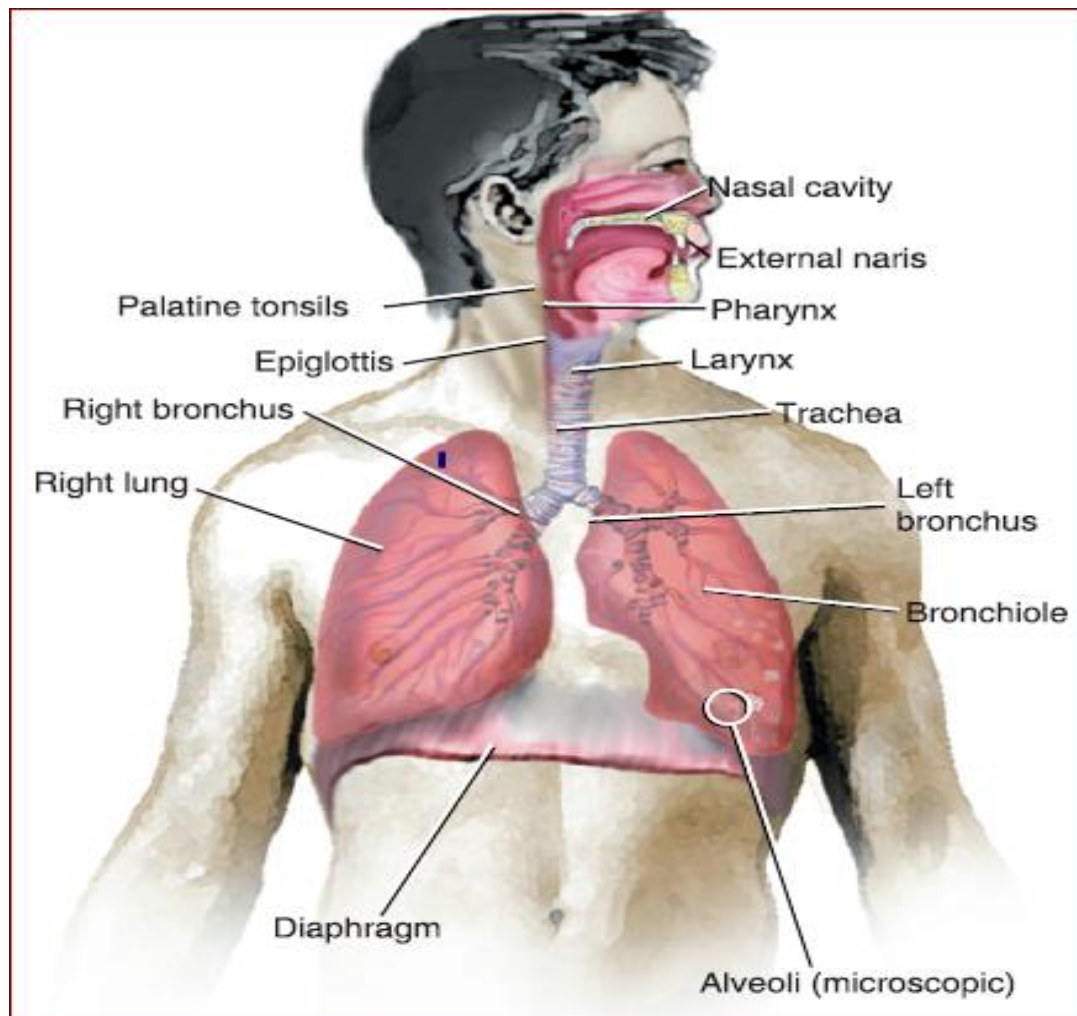
9. Drugs acting on the respiratory system

Dear trainees, upon completion of this chapter, you will be able to:

- ✚ List and categorize drugs used for bronchial asthma and cough
- ✚ Describe the mechanism of action, common adverse effects and contraindications of medications used for asthma and cough.

9.1. Introduction

The respiratory system brings oxygen into the body through inhalation and expels carbon dioxide gas through exhalation.



The respiratory system includes the nasal cavities, pharynx, trachea as well as the bronchi and bronchioles, and the lungs. As air enters into the nose, it is warmed, moistened, and filtered. Inside the lungs, the bronchial tubes branch out and lead to the alveolar sacs that are the site of gas exchange within the lungs. The lungs have specialized tissues called alveoli that are responsible for the exchange of gases between the blood and inhaled air.

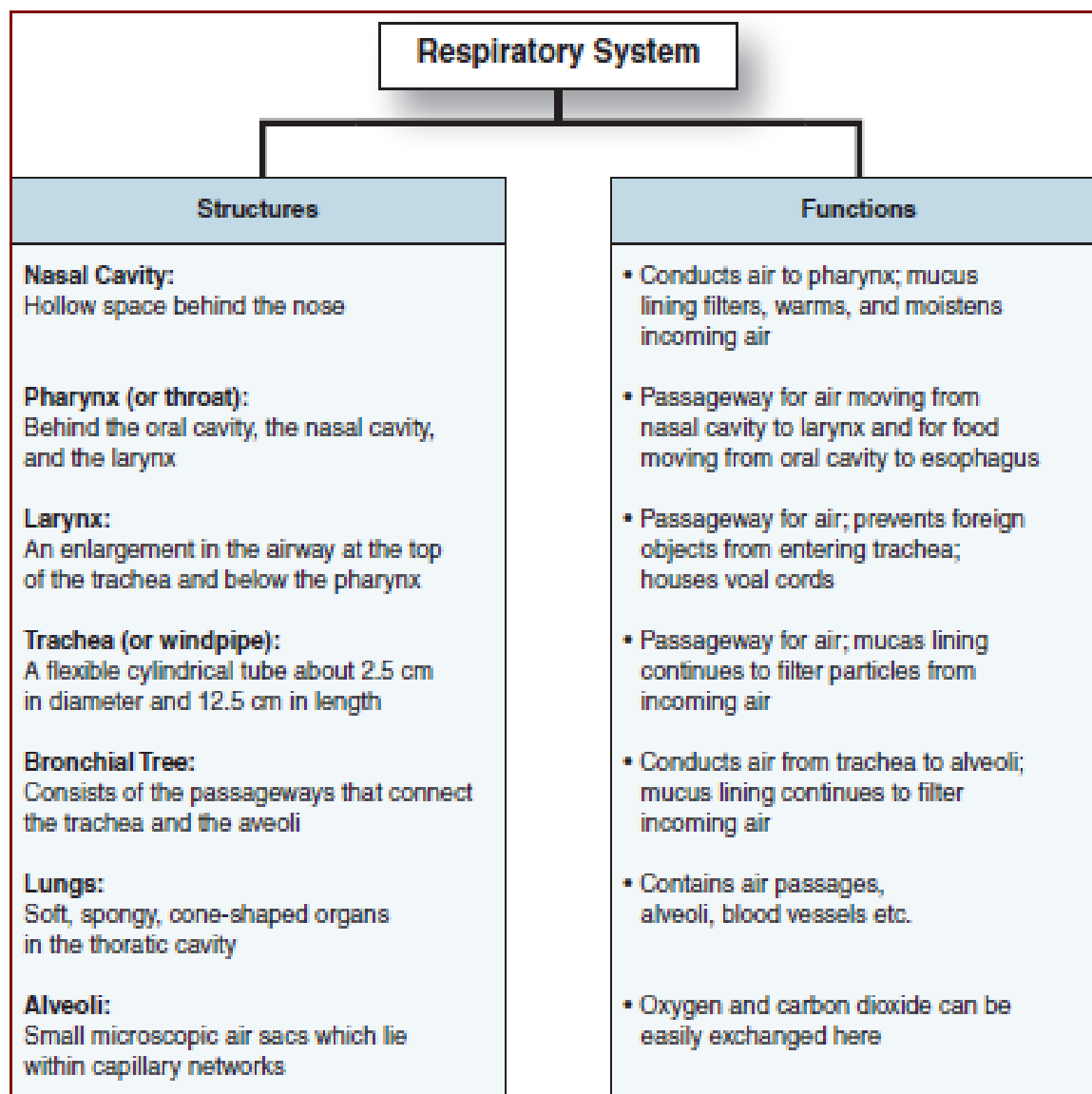


Figure: Respiratory system parts and function

This chapter will focus on drugs used to treat some of the more common disorders affecting the respiratory system particularly bronchial asthma, cough and congestions associated with certain respiratory disorders.

9.2. Drugs for Bronchial Asthma

Asthma is a chronic inflammatory disease of the airways characterized by increased responsiveness of the tracheobronchial tree to allergens and physical stimuli. Clinically it is characterized by episodic shortness of breath, usually accompanied by wheezing and coughing. Common precipitating factors include exposure to cold weather, upper respiratory tract infections, bad smells, exercise, ingestion of drugs like aspirin and beta-blockers etc.

Overall objectives of therapy are to return lung function to as near normal as possible and to prevent acute exacerbations of the disease.

Primary classes of antiasthma drugs are **bronchodilators and anti-inflammatory** agents.

9.2.1. Bronchodilators

- Bronchodilators are used both in maintenance therapy and as needed to reverse acute attacks
- Anti-inflammatory therapy must be used in conjunction with bronchodilators in all but the mildest asthmatics
 - Commonly used anti-inflammatory agents include **hydrocortisone, prednisolone, beclomethasone, triamcinolone**
- **Bronchodilators include:**
 - β - Adrenergic agonists
 - Methylxanthines; theophylline
 - The theophylline preparations most commonly used for therapeutic purposes is aminophylline (theophylline plus diethylamine)
 - Contraindications/cautions: Peptic ulcer disease, seizure disorders, arrhythmias
 - Muscarinic receptor antagonists e.g. Ipratropium bromide

β - Adrenergic agonists

- Non-selective β - agonists eg. Adrenaline (epinephrine)
 - Cause more cardiac stimulation (mediated by a β_1 receptor), they should be reserved for special situation
 - Administered by inhalation or subcutaneously.

- Side effects include arrhythmia and worsening of angina pectoris, increase blood pressure, tremors
- β_2 - selective agonists
 - Largely replaced non-selective β_2 - agonists
 - are effective after inhaled or oral administration and have got longer duration of action
 - Commonly used drugs both by oral and inhalation are
 - Salbutamol, terbutaline, metaproterenol
 - Salmeterol and formeterol are long acting β_2 - selective agonists (with duration of action 12 hrs or more)
 - Side effects
 - Tremors, anxiety, insomnia, tachycardia, headache, hypertension and etc.

Methylxanthines; theophylline, aminophylline

- The theophylline preparations most commonly used for therapeutic purposes is aminophylline (theophylline plus diethylamine)
- Used to treat lung disease that is unresponsive to other medications; used as a bronchodilator in reversible airway obstruction caused by asthma, chronic bronchitis, or emphysema
- MOA: Reverse bronchospasm associated with antigens and irritants; improve contractility of diaphragm
- Contraindications/cautions: Peptic ulcer disease, seizure disorders, arrhythmias
- Special Considerations: Blood levels need to be maintained at 8 to 20 mcg/ml.

9.2.2. Anti-inflammatory

Anti-inflammatory drugs are used both for treatment and prophylactic purposes. They decrease bronchial reactivity and frequency of asthma exacerbation and severity of symptoms. These classes of anti-asthmatic drugs include corticosteroids (which will be discussed under endocrine drugs) and leukotriene inhibitors.

Leukotriene modifiers (Zafirlukast, Montelukast) are a class of biologically active compounds that occur naturally in leukocytes and produce allergic and inflammatory reactions similar to those

of histamine. They are thought to play a role in the development of allergic and autoallergic diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease, and psoriasis.

Indications: - Leukotriene modifiers are used for prophylaxis and chronic asthma in adults and children older than 12 years. Zafirlukast is prescribed as maintenance therapy for patients with chronic asthma. Montelukast is prescribed prophylactically for asthma attacks.

Adverse effect

Montelukast and zafirlukast may produce cough, hoarseness or sore throat, headache, indigestion, heartburn or stomach upset, and runny nose. Montelukast may also produce difficulty sleeping, dizziness, drowsiness, muscle aches or cramps, or unusual dreams.

9.3. Drugs for cough

Cough is a protective reflex, which serves the purpose of expelling sputum and other irritant materials from the respiratory airway.

Types

- Useful productive Cough-Effectively expels secretions and exudates
- Useless cough-Non-productive chronic cough
 - Due to smoking and local irritants

Drug classes used for treatment of cough include

- Antitussives
- Expectorants
- Mucolytics and
- Decongestants

9.3.1. Antitussives

Antitussives are drugs used to suppress the intensity and frequency of coughing.

MOA: Depression of the cough center or suppression of nerve receptors in respiratory system

May be divided into two groups:

- Opioid antitussive e.g. codeine, hydrocodeine, etc
- Opioid derivatives without addiction liabilities: dextromethorphan

Codeine

- Codeine is a narcotic relatively less addicting drug and central antitussive agent
- Nausea, vomiting, constipation, tolerance to antitussive as well as analgesic effects, and physical dependence can occur, but potential for abuse is low.

Dextromethorphan

- Dextromethorphan is an opioid synthetic antitussive, essentially free of analgesic and addictive properties

9.3.2. Expectorants

- + Is a drug that aid in removing thick tenacious mucus from respiratory passages by decreasing their viscosity, thus facilitating removal
- + **Guaifenesin** is the most commonly used expectorant in OTC cough remedies.
- + **Adverse reactions:** Nausea and vomiting, drowsiness, GI distress

9.3.3. Mucolytics

- + Are agents that liquefy mucus and facilitate expectoration
- + **MOA:** Break apart glycoprotein, resulting in a reduction of viscosity and easier movement and removal of secretions.
- + Drugs: Acetylcysteine, bromhexine
- + Acetylcysteine has an unpleasant odor and taste that may cause noncompliance

9.3.4. Decongestants

Decongestants are the drugs that reduce congestion of nasal passages, which in turn open clogged nasal passages and enhance drainages of the sinuses.

Indications: Temporary relief of nasal congestion from the common cold, sinusitis, and upper respiratory allergies

MOA: Stimulation of the α -adrenergic receptors, resulting in constriction of the dilated arteries within the nasal mucosa

- e.g phenylephrine, oxymetazoline and pseudo ephedrine

Adverse reactions: CNS stimulation, increased blood pressure, increased heart rate

- Decongestants should be avoided if the patient has diabetes, heart disease, hypertension, hyperthyroidism, prostatic hypertrophy, or Tourette syndrome.

10. Drugs Affecting the Endocrine System

Dear trainees, at the end of this chapter, you will be able to:

-  **Discuss the effects of endocrine drugs on different organ/systems**
-  **List various types of endocrine drugs available**
-  **Describe the actions, therapeutic uses and adverse effects of common endocrine drugs**

10.1.Introduction

Endocrine system is a system of glands that secrete hormones into the bloodstream. It consists of the glands that secrete hormones, chemicals that assist in regulating body functions.

The endocrine system releases hormones into the bloodstream, which carries chemical messengers to target cells throughout the body. Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. The two regulatory systems, endocrine system and nervous system, are closely interrelated. For example, in several instances, the release of hormones is stimulated or inhibited by the nervous system, some hormones can stimulate or inhibit nerve impulses.

Several organs act as endocrine glands as well as members of other organ systems. For example, the liver, stomach, pancreas, and kidneys are members of the endocrine system as well as other organ systems. Organs that belong primarily to the endocrine system include the pituitary gland, the adrenal glands, the thyroid gland, and the gonads (ovaries and testes).

The pituitary gland produces multiple hormones and is located at the base of the brain. It controls the body's growth and releases hormones into the bloodstream that control much of the activity of the other glands. The thyroid gland is located just below the larynx and releases hormones important for regulating body metabolism. There are four smaller parathyroid glands located on the thyroid gland. The thymus gland is located beneath the sternum. The pancreas is best known for its production of insulin and glucagon. The small adrenal glands are located on top of the kidneys. They produce such hormones as aldosterone, cortisol (hydrocortisone), and androgens

and estrogens. The medulla region of the adrenal glands produces the catecholamines; adrenaline (epinephrine) and noradrenaline (norepinephrine).

The anterior pituitary secretes six hormones. These include growth hormone, prolactin, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, adrenocorticotrophic hormone. The posterior lobe releases two of the pituitary hormones: Antidiuretic hormone (vasopressin) and Oxytocin.

The major body organs affected by endocrine hormone are listed as below table.

Table 10.1: Endocrine Glands, Hormones, and Their Functions and Structure

Organ/tissue	Hormone	Major function
Hypothalamus	Thyrotropin-releasing hormone	Stimulates secretion of Thyrotropin-releasing hormone
	Corticotropin-releasing hormone	Causes release of ACTH
	Growth hormone–releasing hormone	Causes release of growth hormone
	Growth hormone inhibitory hormone (somatostatin)	Inhibits release of growth hormone
	Gonadotropin-releasing hormone	Causes release of LH and FSH
	Dopamine or prolactin-inhibiting factor Growth hormone	Inhibits release of prolactin
Anterior pituitary	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormones (thyroxine)
	Adrenocorticotrophic hormone (ACTH)	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)
	Prolactin	Promotes development of the female breasts and secretion of milk

	Follicle-stimulating hormone (FSH)	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes
	Luteinizing hormone (LH)	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries
Posterior pituitary	Antidiuretic hormone (ADH) (also called vasopressin)	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood pressure
	Oxytocin	Stimulates milk ejection from breasts and uterine contraction
Thyroid	Thyroxine (T4); triiodothyronine (T3)	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracellular fluid calcium ion concentration
Adrenal	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects
	Aldosterone	Increases renal sodium reabsorption, potassium secretion, and hydrogen ion secretion
	Norepinephrine, epinephrine	Same effects as sympathetic stimulation
Pancreas	Insulin (beta-cells)	Promotes glucose entry in many cells, and controls carbohydrate metabolism
	Glucagon (alpha-cells)	Increases synthesis and release of glucose from the liver into the body fluids
Parathyroid	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones

10.2. Antidiabetic drugs

Diabetes Mellitus is a disease that occurs as a result of absolute or relative deficiency of insulin that results in metabolic and vascular abnormalities. Upon ingestion of carbohydrates, insulin is released into the blood and promotes uptake and utilization of glucose in specific organs, namely, the heart, adipose tissue, and skeletal muscle.

The **etiologies** (causative factors) include:

- **Obesity:** chronic calorie intake and prolonged stimulation of β cell causes a decrease in insulin receptor and also adipose tissue and muscle are less sensitive
- Hereditary (from family)
- damage of pancreatic tissue
- diabetogenic hormones (like growth hormone, thyroid, epinephrine),
- diabetogenic drugs like Thiazide diuretics, epinephrine, phenothiazines,
- Other factors: Pregnancy

The common **signs and symptoms** include

- polydipsia, polyphagia, polyuria, dehydration due to glucosuria.

Types of Diabetes mellitus:

- **Type I:** (or Juvenile type) occurs predominantly in children and young adults who have no insulin secretion.
 - It is also called insulin dependent diabetes mellitus (IDDM)
 - Insulin replacement therapy is necessary to sustain life
- **Type II:** (or maturity onset type) usually occur after the age of 40 years.
 - It is also known as non-insulin dependent diabetes mellitus (NIDDM)
 - Characterized by tissue resistance to the action of insulin combined with a relative deficiency in insulin secretion.
- **Gestational Diabetes Mellitus:** Defined as any abnormality in glucose levels noted for the first time during pregnancy.

The **complications** of diabetes mellitus are:

- Ketoacidosis (in types I): is serious complication of diabetes due to insulin deficiency
 - Management includes Regular (soluble) insulin IV infusion
- Hyperglycemic coma (in type II): due to excess dose of insulin
 - Management includes giving glucose or glucagon

- Cardiovascular disorders: Hypertension, atherosclerosis (cholesterol deposits plaques), myocardial infarction, peripheral arterial insufficiency, Anemia, stroke, nephropathy, retinopathy, neuropathy.

Drugs used for treatment of DM include:

Insulin

The goal of insulin therapy is to replicate normal physiologic insulin secretion and replace the background or basal (overnight, fasting, and between-meal) as well as bolus or prandial (mealtime) insulin.

Sources of insulin: naturally from pork or beef, and also human

Actions: lower blood glucose level through increasing utilization of glucose by peripheral tissue and promoting synthesis and storage of glycogen.

Four principal types of injected insulins are available:

- i. Rapid acting, with very fast onset and short duration;
 - **Insulin lispro, insulin aspart, and insulin glulisine**
- ii. short-acting, with rapid onset of action
 - **Regular Insuline**
- iii. intermediate-acting
 - **NPH (neutral protamine Hagedorn, or isophane) insulin; Lente insulin**
- iv. long acting, with slow onset of action
 - **Insulin glargine; Protamine Zn insulin, Insulin detemir**

Table 10.2: Insulin types with their routes of administration

Types	Routes of administration
Regular Insulin	IV, SC, IM
Lente insulin,	SC, IM
Protamine Zn insulin	SC, IM

- ✓ Only regular insulin can be given by intravenous route.

Examples of recommended insulin regimens

- Short acting insulin mixed with intermediate - acting insulin: twice daily (before meals)
- Short acting insulin mixed with intermediate acting insulin before breakfast: Short-acting insulin before evening meal; and Intermediate-acting insulin: at bed time
- Short-acting insulin: three times daily (before breakfast, midday and evening meal)
- Intermediate - acting insulin at bedtime
- Intermediate-acting insulin with or without short-acting insulin once daily either before breakfast or at bedtime suffices for some patients with type II diabetes who need insulin, sometimes in combination with oral hypoglycemic drugs.

The available insulin preparation in Ethiopia:

- Biphasic Insulin
- Biphasic Isophane Insulin (Soluble/Isophane Mixture)
- Insulin Soluble/Neutral
- Insulin Zinc suspension/Insulin Lente
- Insulin lispro/Insulin protamine

Indication:

- Treatment of type I DM,
- Treatment of type II DM not controlled by other agents
- Management of diabetic ketoacidosis
- Control of diabetes in pregnancy, during surgery and in infections

Adverse Reaction and complication:

- **Hypoglycemia** (reduced blood glucose)
- Hypertrophy (increase size) at site of injection
 - Hypersensitivity reaction (insulin allergy)

Oral hypoglycemic drugs

- These are antidiabetic drugs administered orally
- They lower blood glucose level and used in mild diabetes
- They are grouped as: **Sulphonylureas** and **Biguanides**.

Sulphonyl ureas

Preparations and their dosage

- Tolbutamide (Tablet, 500mg): 500 mg before each meal and once or twice per day
- Chlorpropamide (Tablet, 100mg, 250mg): 250 mg daily; single dose in the morning
- Glibenclamide (Tablet, 5mg): 2.5 mg/d-20 mg/d
- Glipizide: Tablet, 2.5mg, 5mg, 10mg
- Gliclazide: Tablet, 30mg, 40mg, 80mg (sustained release)
- Glimperide: Tablet, 1mg, 2mg, 4mg

Indication: management of Mild diabetes mellitus in old patients (type II)

Side effects: Gastric irritation, prolonged hypoglycemia (esp. chlorpropamide), confusion, defect to fetus (contra-indicated in pregnancy)

Drug interaction

- increased hypoglycemia by sulphonamides, phenylbutazone
- added side effect (flushing of the face, severe headache, vomiting etc.) with alcohol, and
- increase in bleeding effect with oral anticoagulant are common drug interaction if used at the same time.

Biguanides

- Biguanides work by preventing the production of glucose in the liver, improving the body's sensitivity towards insulin and reducing the amount of sugar absorbed by the intestines.
 - They potentiate the hypoglycemic action of insulin and sulphonyl ureas
 - The only commercially available biguanides is **metformin**.
 - Metformin is effective as monotherapy (alone) and in combination with nearly every other therapy for type 2 diabetes
 - Combinations of metformin in conjunction with glipizide, and glyburide are available
- Side effects:** Nausea, vomiting, anorexia, diarrhea, abdominal cramp
- Use:** Obese diabetics (uncontrolled by diet alone), Supplement to sulphonyl urea

Drugs that affect absorption of glucose (α -glucosidase inhibitors):

- They delay the digestion and absorption of starch and disaccharides
- **Acarbose** is available
- Dosage of 50 mg twice daily up to 100 mg three times a day.
- It lowers postprandial glucose levels by 30–50%.
- **adverse effects:** flatulence, diarrhea, and abdominal pain

10.3. Drugs for Thyroid disorders

The normal thyroid gland secretes sufficient amounts of the thyroid hormones triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine)—to normalize growth and development, body temperature, and energy levels.

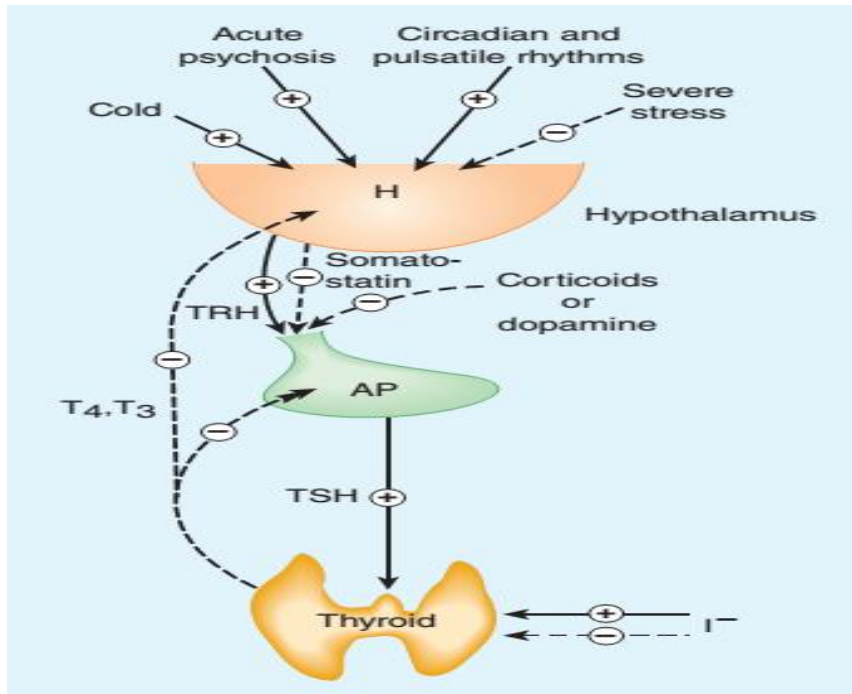


Figure 10.1: thyroid gland regulation and secretion

The hypothalamic-pituitary-thyroid axis. Hypothalamic thyroid-releasing hormone (TRH) stimulates pituitary thyroid-stimulating hormone (TSH) release, while somatostatin and dopamine inhibit it. TSH stimulates T₄ and T₃ synthesis and release from the thyroid, and they in turn inhibit both TRH and TSH synthesis and release. Small amounts of iodide are necessary for hormone production, but large amounts inhibit T₃ and T₄ production and release. Solid arrows, stimulatory influence; dashed arrows, inhibitory influence. H, hypothalamus; AP, anterior pituitary. **Source;** Bertram G. Katzung: Basic & Clinical Pharmacology 13th ed.

Thyroid hormones and anti-thyroid drugs

- Thyroid hormone preparations include: thyroxine sodium
 - Used in hypothyroidism (reduced secretion of thyroid hormones)
- Anti-thyroid drugs include: propylthiouracil, methimazole, carbimazole, Lugol's iodine, potassium iodide, propranolol, metoprolol

Table 10.3: Anti-thyroid and thyroid preparations with their specific indication

Preparation	Indication	Dosage forms	Remarks
Iodine + Potassium Iodide	thyrotoxicosis (pre-operative)	Solution, 5% + 10%	Can decrease the size of the gland
Carbimazole	Hyperthyroidism	Tablet, 5mg	Contraindicated during pregnancy
Propranolol	Tachycardia due to thyrotoxicosis	Injection 1mg/ml in 1ml ampoule, Tablet, 10mg, 40mg	Replaced by metoprolol for asthmatic patients
Propylthiouracil	Hyperthyroidism	Tablet, 25mg, 50mg, 100mg	preferred to carbimazole in pregnancy
Thyroxine Sodium	Hypothyroidism	Tablet, 0.05mg, 0.1mg	

10.4.Female Sex Hormones and Hormonal Contraception

Estrogens

- These drugs can be classified into three groups.
 - a. Natural – estradiol, esterone, estriol
 - Estradiol is most potent
 - b. Semisynthetic – Ethnylestradiol
 - Highly potent, effective orally
 - c. Synthetic: Diethylstibosterol
- Estrogen inhibit release of gonadotrophins (FSH, LH)
- Estrogen causes the growth of gland and duct system

Therapeutic uses:

- contraceptive in combination with progestogens,
- Functional uterine bleeding,

- Dysmenorrhea,
- Alleviation of menopausal disorder,
- Osteoporosis,
- Replacement therapy in ovarian failure,
- Prevents senile and atrophic vaginitis

Side effects:

- Thromboembolism, Sodium and water retention, Withdrawal bleeding, nausea, endometrial carcinoma

Progestogens

- Progesterone is natural occurring progestational hormone.
- It is synthesized by corpus luteum, placenta, adrenal cortex, and testis.
- It is given through intramuscular route.
- Progestogens inhibits ovulation
- It also causes relaxation of the uterus in late pregnancy

Synthetic /Semisynthetic progestogens:

- Derivative of progesterone: Hydroxyprogesterone capriote/medroxyprogesterone
- Derivative of testosterone: Dimethisterone
- Nortestosterone: Norethisterone

Therapeutic use: they are indicated for purpose of:

- Contraception (pregnancy prevention),
- Stopping of functional uterine bleeding
- Relief from dysmenorrhea, and Amenorrhea,
- Reduction of Endometrial Carcinoma

Hormonal contraceptives

Oral Contraceptives (OC)

- These are drugs taken orally to prevent conception
- Combined regimen: involves
 - The administration of pills containing combination of Estrogen and Progestogen.
 - They are administered starting 5th day of menstrual cycle for 21 days.

- Fixed dose combination: the commonest procedure is to administer one pill containing both an estrogen and progestin daily at bed time for 21 days.
- In biphasic and triphasic pills: these are combined oral contraceptive pills containing varying proportion of an estrogen and progesterone designed to stimulate the normal pattern of menstrual cycle.

Single Entity preparation

- ❖ Continuous progestrone: it makes cervical mucus thick and also alter endometrial wall
 - Oral progesterone: Norethindone (Norgestril)
 - Depot (IM injection) e.g. Medroxyprogesterone acetate (Depoprovera ®)
 - Subcutaneous implant: L- norgestril (Norplant®)
- ❖ Post coital “morning after” pill: used within 72 hrs after unsafe sexual intercourse
 - Oestrogen like Diethyl stilbesterol
 - Combined oral contraceptive pills can also be used.
 - L-Norgestrel: 0.75 mg twice daily for 1 day is commonly used

Side effects of OC:

- Thromboembolic complication
- Weight gain & fluid retention
- Menstrual disorder, Breast tenderness & fullness, Reduced lactation
- Skin changes, Nausea & vomiting; depression

Contraindication of OC: the drug is not used for patient with the below condtions

- In patients with cardiovascular diseases (hypertension, coronary heart disease)
- Thromboemolic disease, diabetes mellitus, liver disease
- breast Cancer
- women > 35 years (esp. smokers and hypertensives)

10.5.Obstetric and gynecological medications

Mifepristone, Clotrimazole, Ergometrin, Magnesium sulphate, Misoprostol, Misoprostol + Mifepristone, Pethidine, Dinoprostone (Prostaglandine E2), Oxytocin

MIFEPRISTONE: its major use thus far has been to terminate early pregnancies (**abortion**) in combination with **misoprostol**.

OXYTOCICS: are oxytocin, Prostaglandins, and Ergometrin which are used to cause contraction of the uterus and milk ejection.

- **Oxytocin:** used to induce labor by stimulating the uterus contraction. It also causes ejection of milk through contraction of the mammary gland.
- **Prostaglandins:** induce labor at any time during pregnancy
- **Ergometrine:** Prevent bleeding after delivery of placenta if bleeding is severe by causing sustained uterine contraction

Magnesium sulphate: Prevention of convulsion in **eclampsia** (hypertension during pregnancy)

Pethidine hydrochloride: analgesia (relief of pain) during labour.

Clotrimazole: for vaginal candidiasis treatment

Dinoprostone (prostaglandin E2): Terminate pregnancy and evacuate uterus in cases of missed abortion or intrauterine fetal death

Group activity: Be in small groups discuss the following points

- ® Selection of contraceptive for different length of pregnancy prevention
- ® Selection of route of administration depending on individual interest and provide recommendation

10.6. Drugs for the treatment of erectile dysfunction

Erectile dysfunction (ED) is managed by the administration of drugs that promote penile engorgement and slow loss of erection. This control is orchestrated by relaxation and contraction of the smooth muscle in the corpus cavernosum. Neurotransmitters of the autonomic nervous system and nonadrenergic, noncholinergic system control relaxation and contractions. Nitric oxide is a mediator of smooth muscle relaxation that is released by the nonadrenergic noncholinergic system as a response to sexual stimulation. It activates several intracellular enzymes; phosphodiesterase type 5 (PDE5), an enzyme involved in the reversal of an erection, is an example.

The most commonly prescribed drugs for the treatment of erectile dysfunction are PDE5 inhibitors. Phosphodiesterase Inhibitors include Sildenafil, tadalafil, and vardenafil. They are taken prior to

intercourse to produce an erection. Sildenafil and tadalafil are taken 30 minutes prior to intercourse. Vardenafil is taken up to 60 minutes before sexual activity.

Many of the adverse reactions associated with the use of phosphodiesterase inhibitors are a result of vasodilation. These side effects include dizziness, flushing, headache, and nasal congestion. Gastrointestinal side effects are diarrhea and indigestion. Sildenafil, tadalafil, and vardenafil may also produce visual effects that range from light sensitivity and difficulty distinguishing between green and blue to loss of vision. The incidence of visual disturbances is greater with sildenafil than with vardenafil and tadalafil.

10.7.Corticosteroids

Ψ Control the metabolism of carbohydrate (CHO), protein, fat and water /electrolytes

Ψ They include **glucocorticoids** and **mineralocorticoids**

- **Glucocorticoid:** regulate carbohydrate metabolism
 - Examples: Cortisone, Hydrocortisone (Cortisol)
- **Mineralocorticoid:** regulate electrolyte balance
 - Examples: Aldosterone, Deoxycorticosterone

Practice exercise I: Choose the best answer for the following questions

1. Which of the following is the treatment of choice for hypothyroidism?
 - A. Iodide B. Levothyroxine C. propranolol D. Propylthiouracil
2. Select the correct statement regarding ketoacidosis
 - A. Ketoacidosis is complication due to excess of insulin in the body
 - B. ketoacidosis is treated by insulin administration
 - C. ketoacidosis is common for type I
 - D. it is treated by using glucose infusion
3. which types of insulin is administered three times daily
 - A. Short acting insulin mixed with intermediate acting insulin
 - B. Intermediate - acting insulin
 - C. Short-acting insulin

- D. Long acting insulin
4. Which of the following drugs is **not used** in management of diabetes mellitus?
- A. Insulin B. Glimperide C. Glucagon D. Metformin
5. The most common adverse effect of anti-diabetic drug is:
- A. Hyperglycemia C. Hypoglycemia
B. Obesity D. Loss of appetite
6. The drugs that are used for prevention of pregnancy (contraceptive) are
- A. Estrogen C. Levonorgestrol
B. Progesterone D. All of the above
7. The route of administration of contraceptive drugs include *except*:
- A. Oral route C. Subcutaneous patch
B. Intramuscular route D. None of the above
8. _____ not used Obstetric and gynecological condition.
- A. Oxytocics
B. Mifepristone
C. Magnesium sulphate
D. Oral contraceptives

Practice exercise II: Match the specific drug under B to their class listed under category A

A

1. Antithyroids drug
2. Antidiabetic drug
3. Contraceptive drug
4. Obstetric and Gynecological drug
5. Corticosteroid drug

B

- a) Hydrocortisone
- b) Propyl thiouracil
- c) Insulin preparation
- d) Medroxyprogesterone acetate
- e) Misoprostol

11. Chemotherapeutic agents

Dear trainees, at the end of this chapter, you will be able to:

-  **List common pathogenic microorganisms**
-  **Describe principle of chemotherapy**
-  **List commonly used antibacterial, antifungal, antiviral, antiprotozoal and antihelmintics drugs**
-  **Describe indications, common adverse effects, major contraindications and significant interaction of chemotherapeutic agents**

11.1.Introduction to pathogenic organisms

It would be difficult to overstate the impact of disease on history. Since the beginning of human existence on the planet, diseases have played a significant role in the events of every era. Malaria, one of the oldest known diseases, caused drastic declines in the population of Greek city-states in the fourth century. The Spanish flu epidemic of 1918–1919 killed 20 million people around the world — more than twice the number of people who were killed during World War I. In 1944, a major outbreak of polio in USA overwhelmed the area's medical facilities, separating sick children from their families and preventing healthy young people from visiting each other for fear of contracting the disease.

Scientific achievements through the ages have greatly alleviated the effects of some of the worst diseases through invention of antibiotics, formulation of vaccines and advent of effective mosquito control, and the introduction of modern sanitation.

Pathogenic Microorganisms

Micro-organisms are creatures that are not directly visible to the naked eyes. They are detected by using a microscope. A branch of biology which studies about microorganisms is called microbiology.

Most microorganisms are actually beneficial to our body, for example, by aiding in the process of digestion. However, there are microorganisms that are damaging to human being, either by the production of toxic products, or direct infection and these microorganisms are termed pathogenic.

Pathogenic microorganisms cause infectious diseases. Infectious diseases are communicable and transmitted by insects, animals and by taking contaminated food and water. Chickenpox, measles and typhoid are some of the infectious diseases. Some of the infectious microbes can also cause cancer; for example, Human papillomavirus causes cervical cancer.

An opportunistic infectious disease is caused when there is weak immune system. Opportunistic disease is not observed in a healthy individual that has a normal immune system, but observed in patients with weak immunity. Immunity can be weak when there is malnutrition, ageing, HIV/AIDS. Drugs such as corticosteroids can also weaken immunity.

Pathogenic microorganisms include **bacteria, fungi, viruses, protozoa and helminths** (worms). All bacteria are prokaryotes, and fungi, protozoa, helminths are eukaryotes. Eukaryotic cells contain a true nucleus, whereas prokaryotic cells contain a nucleoid without a nuclear membrane.

Infectious diseases are clinically diagnosed by laboratory tests such as blood tests, urine tests or stool tests.

Bacteria

Gram staining

In microbiology, the visualization of bacteria at the microscopic level is facilitated by the use of stains, which react with components present in some cells but not others. This technique is used to classify bacteria as either Gram-positive or Gram-negative depending on their color following a specific staining procedure originally developed by a scientist Hans Christian Gram in the 1800s. The reason bacteria are either Gram-positive or Gram-negative is due to the structure of their cell envelope.

Gram positive bacteria have a thick peptidoglycan layer in their cell wall, which retains the crystal violet during Gram staining, resulting in a purple color/ crystal violet. **Common pathogenic gram-positive bacteria include:** Actinomyces, Clostridium, corynebacterium, Enterococcus, Lactobacillus, Listeria, Mycobacterium, Nocardia, Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae, streptococcus pyogenes

Gram negative bacteria have a thin peptidoglycan layer which does not retain the crystal violet, so after washing, a counterstain (safranin) they stain red/ pink. **Common Gram-negative Bacteria include** Escherichia coli, Pseudomonas aeruginosa, Neisseria gonorrhoeae, Chlamydia trachomatis, Salmonella typhi, Enteritis Salmonella, Enterobacteriaceae, Moraxella catarrhalis, Haemophilus influenzae Helicobacter pylori, Treponema pallidum, Neisseria meningitidis, Klebsiella pneumoniae, Legionella pneumophila, Vibrio cholerae.

Acid-fast bacteria: seen under the microscope following a staining procedure in which the bacteria retain the color of the stain after an acid wash (acid-fast). Good example for acid fast bacteria is **Mycobacterium tuberculosis**

Atypical bacteria are bacteria that do not color with gram-staining but rather remain colorless: they are neither Gram-positive nor Gram-negative. These include the mycoplasma, Rickettsia, spirochetes, chlamydia, legionella.

Mycoplasma - all bacteria are characterized by a cell wall outside cell membrane; however, mycoplasma is unique as it lacks a cell wall that is also considered a protective mechanism that makes it easier for bacteria to evade antibiotic therapies. It is a causative agent for life-threatening pulmonary infections and some strains may cause pelvic disease.

The rickettsia is diverse collection of intracellular Gram-negative bacteria found in ticks, lice, fleas, mites, chiggers, and mammals. They cause disease like Rocky Mountain spotted fever and epidemic typhus. Symptoms usually include sudden-onset fever with severe headache, malaise, prostration, and, in most cases, a characteristic rash. Common pathogenic species: R. rickettsii, R. prowazekii, R. typhi

Chlamydia trachomatis causes a common sexually transmitted disease called chlamydia. Chlamydia doesn't usually cause any symptoms.

Spirochetes cause diseases like relapsing fever, Lyme disease and syphilis. Relapsing fever is characterized by recurring episodes of fever separated by periods of relative well-being and caused by *Borrelia recurrentis*. Lyme disease is caused by *Borrelia burgdorferi*. Ticks pick up the spirochete by sucking the blood of infected animals. Syphilis is caused by *Treponema pallidum*. Syphilis is usually a sexually transmitted disease.

Legionella pneumophila causes Legionnaires' disease, a severe form of pneumonia (lung inflammation). Most people get Legionnaires' disease from inhaling the bacteria. Symptoms include: headache, muscle pain, chills, fever, cough which may bring up mucus and sometimes blood, shortness of breath, chest pain, nausea, vomiting and diarrhea, confusion or other mental changes. This often begins two to ten days after being exposed.

Based on their ability to use oxygen bacteria can be classified into:

- **Aerobic bacteria:** bacteria that can survive and grow in an oxygenated environment
- **Anaerobic:** bacteria that does not require oxygen for growth. It may react negatively or even die if oxygen is present.

Fungi

Pathogenic fungi are fungi that cause disease in humans or other organisms. Approximately 300 fungi are known to be pathogenic to humans. The study of fungi pathogenic to humans is called "medical mycology". Although fungi are eukaryotic, many pathogenic fungi are microorganisms.

The following are common pathogenic fungal agents:

- **Candida albicans** is a kind of diploid yeast that commonly occurs among the human gut microflora. *C. albicans* is an opportunistic pathogen in humans. Abnormal overgrowth of this fungus can occur, particularly in immunocompromised individuals.
- **Aspergillus fumigatus and Aspergillus flavus:** *Aspergillus flavus* produces aflatoxin which is both a toxin and a carcinogen and which can potentially contaminate foods such as nuts. *Aspergillus fumigatus* can cause allergic disease. Aspergillosis is the group of diseases caused by *Aspergillus*. The symptoms include fever, cough, chest

pain or breathlessness. Usually, only patients with weakened immune systems or with other lung conditions are susceptible.

- **Cryptococcus neoformans** can cause a severe form of meningitis and meningo-encephalitis in patients with HIV infection and AIDS.
- **Histoplasma capsulatum** can cause histoplasmosis in humans, dogs and cats. Infection is usually due to inhaling contaminated air.
- **Pneumocystis jirovecii (or Pneumocystis carinii)** can cause a form of pneumonia in people with weakened immune systems, such as premature children, the elderly and AIDS patients.

Topical fungal infections include the following:

- ✓ **Trichophyton rubrum:** causes **Tinea cruris**, a dermatophyte fungal infection of the groin region in any sex, though more often seen in males. It also causes Tinea pedis, dermatophyte infection of the soles of the feet and the interdigital spaces.
- ✓ As the common name for this condition implies, it causes itching or a burning sensation in the groin area, thigh skin folds or anus. It may involve the inner thighs and genital areas, as well as extending back to the perineum and perianal areas.
- ✓ **Microsporum audouinii, Trichophyton tonsurans, Trichophyton violaceum:** these fungal species cause **Tinea capitis** is a cutaneous fungal infection (dermatophytosis) of the scalp. It may appear as thickened, scaly, and sometimes boggy swellings, or as expanding raised red rings (ringworm). Common symptoms are severe itching of the scalp, dandruff, and bald patches where the fungus has rooted itself in the skin.
- ✓ **Tinea corporis** (also known as ringworm) is a superficial fungal infection (dermatophytosis) of the arms and legs, especially on hairless skin. It may have a variety of appearances; most easily identifiable are the enlarging raised red rings with a central area of clearing (ringworm). Tinea corporis is caused by a tiny fungus known as dermatophyte.

Viruses

Viruses cannot reproduce outside human body; they reproduce if they enter into human cells.

Common viral infections include hepatitis, HIV

Protozoa

Protozoa are unicellular organisms that infect almost every tissue within the body. They can function either as intracellular parasites, or extracellular parasites in the blood, urogenital region, or intestine. Transmission is generally by ingestion of infected food, or by an insect bite.

Common protozoal infections include amoebiasis, giardiasis and malaria.

Helminthes

Helminthes are a group of multicellular, complex worms that live as parasites. They receive their nutrition by ingesting body fluids or tissues, or feeding on digested matter in the gastrointestinal system.

They can be divided into 3 types: Cestodes (e.g. Tapeworms), Trematodes (e.g. Flukes) and Nematodes (e.g. Roundworms)

The **source of pathogenic** microorganisms may be

- Animal
- Airborne (e.g. Tuberculosis, Pneumonia)
- blood borne (e.g. Malaria, Hepatitis)
- Sexual contacts (HIV, Gonorrhea)
- Foodborne
- Soil borne
- Vegetables and fruits

Prevention of infection

- Hand hygiene is important in clinics, health centers and hospitals, before and after patient contact.
- Hand hygiene is also the most effective preventive measure in the home, when handling food, after using the toilet, after handling nasal secretions or sputum, and before or after providing care to children, sick relatives, or other close contacts with risk of predisposing you to infection.
- Vaccination is another potent tool; for example, for meningitis, hepatitis, tuberculosis etc.

11.2.Principle of chemotherapy

Antimicrobial drugs are among the most commonly used and misused of all drugs. The widespread use of antimicrobial drugs has been associated with emergence of antimicrobial-resistant pathogens. Reducing inappropriate antimicrobial use is thought to be the best way to control emergence of resistance. Some basic terminologies and principles of chemotherapeutic drug use are described below.

Terminologies

Chemotherapy: - The use of chemicals against invading organisms (e.g. bacteria) or/and cancer cell.

Antibiotics: - a chemical that is produced by one microorganism and has the ability to harm other microbes. But the term antimicrobials describe both microbial origin, and synthetic drugs.

Selective Toxicity: - is defined as the ability of a drug to injure a target cell or target organism without injuring other cells or organisms that are in intimate contact with the target.

Antimicrobial spectrum: - The scope that a drug kills or suppresses the growth of microorganisms

- **Narrow-spectrum:** The drugs that only act on one kind or few strain of bacteria.
- **Broad-spectrum:** The drugs that kill or inhibit a wide range of microbial strain or species

Bacteriostatics: - drugs that interfere with growth or replication of the microorganism but do not kill it.

Bacteriocidals: - drugs kill bacteria at drug serum levels achievable in the patient

Drug resistance: The ability of bacteria and other microorganisms to resist the effects of a drug to which they were once sensitive. Drug resistance may be acquired by

- **Mutation and selection,** with passage of the trait vertically to daughter cells
- **Horizontal transfer** of resistance determinants from a donor cell to recipient species

Mechanisms of drug resistance can be broadly divided into three groups:

1. Inactivation of the antimicrobial agent either by disruption of its chemical structure or by addition of a modifying group that inactivates the drug
2. Restriction of entry of the drug into the bacterium by altered permeability or efflux pump
3. Modification of the bacterial target – this may take the form of an enzyme with reduced affinity for an inhibitor, or an altered organelle with reduced drug-binding properties

Activity 1

Be in a pair and discuss the following question

Does the Amount of Antibiotic Use Influence the Emergence of Resistance?

The following approaches can delay emergence of drug resistance

-  Prevent infection
-  Diagnose and treat infection effectively
-  Use antimicrobials wisely and when necessary
-  Prevent transmission

Selection of Antimicrobial Agents

When treating infection, the therapeutic objective is to produce maximal antimicrobial effects while causing minimal harm to the host. To achieve this goal, we must select the most appropriate antibiotic for the individual patient. Selection of the most appropriate antimicrobial agent requires knowledge of

- The organism's identity
- The organism's susceptibility to a particular agent
- The site of the infection
- Patient factors
- The safety of the agent, and
- The cost of therapy.

Therapy with antibiotic combinations

Therapy with a combination of antimicrobial agents is indicated only in specific situations. Combination of antimicrobials may be recommended in the following situations.

- ✚ Initial Therapy of Severe Infection.
- ✚ Mixed Infections.
- ✚ Prevention of Resistance.
- ✚ Decreased Toxicity.
- ✚ Enhanced Antibacterial Action.

General principles of prophylactic use of chemotherapy

On a few occasions it is appropriate to use antibacterial drugs prophylactically

- a) Prophylaxis should be restricted to cases where the procedure commonly leads to infection, or where infection, although rare, would have devastating results
- b) The antimicrobial agent should preferably be bactericidal and directed against the likely pathogen
- c) The aim is to provide high plasma and tissue concentrations of an appropriate drug at the time of bacterial contamination.

Misuses of antimicrobial drugs

- ✚ Attempted Treatment of Untreatable Infection
- ✚ Treatment of Fever of Unknown Origin
- ✚ Improper Dosage
- ✚ Treatment in the Absence of Adequate Bacteriologic Information
- ✚ Omission of Surgical Drainage

Imperative: -patients should be instructed to take their medication for the entire prescribed course even though symptoms may subside before the full course has been complete

Classification of antimicrobial drugs by susceptible organisms

- **Antibacterials, antivirals, anti-protozoals, anti-fungals and anti-helminths**

11.3. Anti-bacterial drugs

Antibacterial agents include:

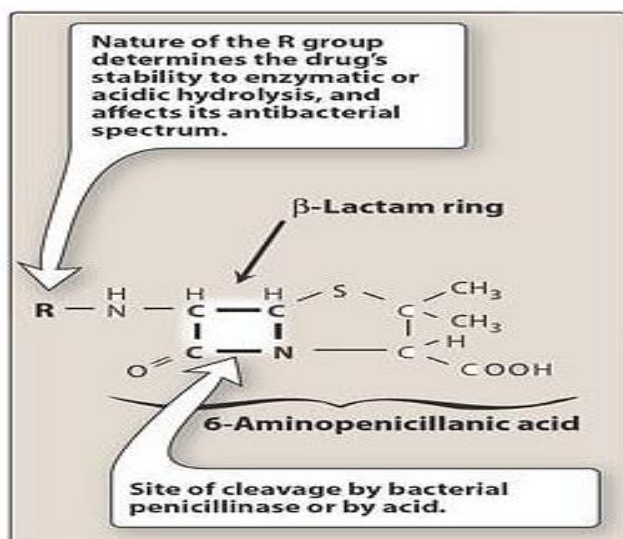
- Cell-wall synthesis inhibitors: Penicillins, Cephalosporins
- Protein synthesis inhibitors: Tetracyclines, Aminoglycosides, Macrolides
- Fluoroquinolones
- Sulfonamides and trimethoprim

11.3.1. Bacteria cell wall synthesis inhibitors (β -lactam antibiotics)

These drugs each contain a β -lactam ring. These drugs share a common structure and mechanism of action i.e. disruption of the bacterial cell wall.

Include:

- Penicillin,
- Cephalosporins,
- Carbapenems and
- Monobactam



Penicillin

The penicillins are among the most widely effective antibiotics and also the least toxic drugs known, but increased resistance has limited their use. In 1928 - Alexander Fleming observed the antibacterial effects of Penicillin and in 1940 - Florey and Chain extracted Penicillin.

Classification

The most useful classification of penicillins is based on antimicrobial spectrum. Penicillins fall into four major groups:

- Natural penicillins
 - ✓ Penicillin G, Penicillin V
- Penicillinase-resistant penicillins
 - ✓ Dicloxacillin, Nafcillin, Oxacillin, cloxacillin, methicillin
- Aminopenicillins (broad spectrum penicillins)
 - ✓ Amoxicillin, Ampicillin
- Extended-spectrum penicillins
 - ✓ Carbenicillin, Piperacillin, Ticarcillin

A. Natural penicillin

Penicillin G (benzylpenicillin) was the first penicillin available and will serve as our prototype for the penicillin family. Penicillin G is active against most gram-positive bacteria (except penicillinase-producing staphylococci), gram-negative cocci (*Neisseria meningitidis* and non-penicillinase-producing strains of *Neisseria gonorrhoeae*), anaerobic bacteria, and spirochetes (including *Treponema pallidum*).

Penicillin G is available as three salts: (1) potassium penicillin G (crystalline penicillin), (2) procaine penicillin G and (3) benzathine penicillin G.

Clinical use

- Penicillin G is drug of choice for:
 - pneumonia or meningitis by *Streptococcus pneumonia*
 - Pharyngitis by *streptococcus pyrogenes*
 - Infectious endocarditis by *streptococcus viridians*
- Penicillin is a preferred agent for infections caused by several gram-positive bacilli, specifically, gas gangrene (caused by *Clostridium perfringens*), tetanus (caused by *Clostridium tetani*), and anthrax (caused by *Bacillus anthracis*). First choice for meningitis by *N. meningitides*
- Penicillin is the drug of first choice for meningitis caused by *N. meningitidis* (meningococcus)
- Drug of choice for the treatment of syphilis

B. Penicillinase-resistant penicillins

Are semi-synthetic antibiotics resistant to staphylococcal penicillinase (hence effective against streptococci and most community-acquired penicillinase- producing staphylococci). Are relatively stable in acidic medium and have reasonable bioavailability. However, food interferes with absorption, and the drugs should be administered 1 hour before or after meals. Generally, less active against Pen G susceptible organisms than other penicillins and they are not useful against gram-negative bacteria

C. Aminopenicillins

In addition to streptococcal (including pneumococcal) strains, ampicillin and amoxicillin are also effective against many strains of *Haemophilus influenzae*, *E. coli*, *Streptococcus faecalis* and *Salmonella*. They are used for a variety of chest infections (e.g. bronchitis, pneumonia), otitis media, urinary tract infections, biliary infections and the prevention of bacterial endocarditis

(amoxicillin). Amoxicillin is somewhat more potent than ampicillin, penetrates tissues better and is given three rather than four times daily. Both are susceptible to β lactamases.

Resistance to these antibiotics is now a major clinical problem because of inactivation by penicillinase. Today they are combined with Clavulanic acid, sulbactam, or tazobactam, which inhibit penicillinase that inactivate the drug.

D. Extended-spectrum penicillins

Semisynthetic penicillins with wider spectra of activity than the other penicillins. Are active against some isolates of *P. aeruginosa* and certain *Proteus* spp. that are resistant to ampicillin and its congeners. Sensitive to destruction by β -lactamases and are generally less effective against gram (+) infections than the other penicillins. Their use is generally limited to treatment of serious infections caused by susceptible gram (-) bacilli or mixed aerobic-anaerobic infections

Adverse Reactions

Hypersensitivity reactions

- 0.7% and 4% of all treatment courses
- Maculopapular rash, urticarial rash, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis, Stevens-Johnson syndrome, and anaphylaxis

Other adverse reactions

- bone marrow depression, granulocytopenia,
- Pain and sterile inflammatory reactions at the sites of intramuscular injections
- Nausea, vomiting, diarrhea, Super infection (antibiotic associated enterocolitis)
- Sodium overload, inhibition of platelet function (ticarcillin)

Cephalosporins

Are derivatives of 7-aminocephalosporanic acid. for the first time isolated in 1948 by Brotzu from the sea near a sewer outlet off the Sardinian coast.

Classification

Classification is based on general features of antimicrobial activity. Four generation based on spectrum of activity

- First generation: - Cefadroxil, cefazolin, cephalixin, Cephalothin
- Second generation: - Cefaclor, Cefprozil, Cefuroxime, Cefoxitin
- Third generation: - Cefdinir, Cefixime, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftriaxone, Cefditoren
- Fourth generation: - Cefepime, Cefpirome

Cephalosporins are formulated for oral, intramuscular, and intravenous use. All except one third generation cephalosporin (cefixime) is administered parenterally and only two second-generation cephalosporins are available for oral use (cefaclor, cefuroxime).

First generation cephalosporins

So-called first-generation cephalosporins are effective against *Streptococcus pyogenes* and *Streptococcus pneumoniae*, *E. coli* and some staphylococci. Their pharmacology is similar to that of the penicillins.

Second generation cephalosporins

Have a broader spectrum than do the first-generation agents and are active against *Enterobacter* spp., indole-positive *Proteus* spp., and *Klebsiella* spp. All second-generation cephalosporins are less active against gram-positive bacteria than the first-generation drugs; Can be given orally or parenterally.

Clinical Uses: Sinusitis, otitis media, or lower respiratory tract infections, mixed anaerobic infections, and community-acquired pneumonia, for prophylaxis in colorectal surgery, in situations where facultative g (-) and anaerobes are involved (intra-abdominal infections, pelvic inflammatory disease, and diabetic foot infection)

Third generation cephalosporins

Antimicrobial activity: The major features of these drugs are the ability of some to cross the blood-brain barrier and their expanded gram-negative coverage (active against *Citrobacter*, *Serratia marcescens*, *Providencia*, and beta-lactamase-producing strains of *Haemophilus* and *Neisseria*).

Of the third-generation cephalosporins, **ceftazidime**, **ceftriaxone** and **cefotaxime** are useful in severe sepsis, especially because (unlike earlier cephalosporins) they penetrate the blood–brain barrier well and are effective in meningitis

Adverse effects

About 10% of patients who are allergic to penicillins are also allergic to cephalosporins. Some first-generation cephalosporins are nephrotoxic, particularly if used with **furosemide**, aminoglycosides or other nephrotoxic agents. Some of the third-generation drugs are associated with bleeding due to increased prothrombin times, which is reversible with vitamin K.

NB: - Persons who are allergic to penicillin may also be allergic to cephalosporins.

Other cell wall synthesis inhibitors

- a) Carbapenems: - includes Imipenem (with cilastatin); Meropenem, and Ertapenem
Are used for serious hospital acquired and mixed bacterial infection treatment
- b) Monobactams: - includes Aztreonam used only for gram-ve bacterial infection
- c) Vancomycin: - It has been lifesaving in the treatment of methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis* infections as well as enterococcal infections.

Activity: Match each antibiotic drug listed below with their appropriate classes

Ampicillin, Aztreonam, Cefotaxime, Cefotetan, Ceftazidime, Ceftriaxone, Cloxacillin, Ticarcillin, penicillin G, cefuroxime

11.3.2. Protein Synthesis Inhibitors

Aminoglycosides

Include: - Gentamicin, Tobramycin, Amikacin, Netilmicin, Kanamycin, Streptomycin, Neomycin

Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli. However, because their use is associated with serious toxicities,

they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation cephalosporins.

Mechanism of action and Pharmacokinetics

Aminoglycosides inhibit bacterial protein synthesis. Aminoglycosides are not absorbed systemically when administered by mouth. The only aminoglycoside that is administered orally (neomycin) is used to reduce the bacteria in the bowel prior to colorectal surgery. Other non-parenteral use is topical application for skin, eye, and ear infections.

Clinical uses

Aminoglycosides are used in serious infections including septicemia, sometimes alone but usually in combination with other antibiotics (penicillins or cephalosporins). **Gentamicin** is widely used and has a broad spectrum, but is ineffective against anaerobes, many streptococci and pneumococci. Creams, ointments, or solutions of gentamycin sulfate are used for the treatment of infected burns, wounds, or skin lesions.

Adverse effects

These are important and are related to duration of therapy and trough plasma concentrations. They are more frequent in the elderly and in renal impairment. Serious adverse reactions are linked to aminoglycoside use including hearing loss (ototoxicity) and kidney damage (nephrotoxicity). These effects limit their use to the treatment of serious infections.

Tetracyclines

Tetracycline includes tetracycline, oxytetracycline, doxycycline, minocycline demeclocycline. They are broad spectrum antibacterial drugs.

Mechanism of action and Pharmacokinetics

Tetracyclines inhibit protein synthesis. Tetracycline interacts with dairy products, calcium, aluminum, and ferrous supplements to form a chelated complex. The complex significantly reduces the absorption of tetracycline and should be avoided. Doxycycline and minocycline are more stable in the acidic stomach contents than tetracycline. They also have a longer duration of action. They are given once or twice daily compared with tetracycline, which is given four times daily.

Clinical use

Tetracyclines have a broad range of antibacterial activity covering both Gram-positive and Gram-negative organisms and, in addition organisms such as Rickettsia, Chlamydia and Mycoplasma. They are used in atypical pneumonias and chlamydial and rickettsial infections, and remain useful in treating exacerbations of chronic bronchitis or community-acquired pneumonia. Tetracyclines are used in the long-term treatment of acne.

Adverse effects

- Nausea, vomiting and diarrhoea
- Hypersensitivity reactions
- Worsening of renal failure
- Hepatotoxicity (rare)
- Discoloration and damage of the teeth and bones of the fetus if the mother takes tetracyclines after the fifth month of pregnancy, and of children; they should therefore be avoided in pregnancy and children under 12 years.

Macrolides

Macrolide antibiotics (e.g. **erythromycin**, **clarithromycin**, **azithromycin**) have an antibacterial spectrum similar, but not identical to that of **penicillin**.

Mechanism of action

Macrolides bind to bacterial 50S ribosomes and inhibit protein synthesis.

Therapeutic uses

Erythromycin

- Legionella pneumophila pneumonia (legionnaires' disease).
- Whooping cough (Bordetella Pertussis)
- Corynebacterium diphtheriae (Diphtheria)
- Chlamydia trachomatis infections (500 mg PO qid for 7 days) and
- as an alternate therapy for syphilis in PCN-allergic patients
- Erythromycin remains useful for treatment of Campylobacter gastroenteritis in children

Clarithromycin

- has a spectrum of antibacterial activity similar to that of erythromycin, but it is also effective against *Haemophilus influenzae*.
- It is commonly used to treat bronchitis, sinusitis, otitis media, pharyngitis, soft tissue infections, and community-acquired pneumonia.
- It has a prominent role in treating MAC infections in HIV patients and is an important component of regimens used to eradicate *Helicobacter pylori*

Azithromycin

- less active against streptococci and staphylococci than erythromycin, but is far more active against respiratory infections due to *H. influenzae* and *Moraxella catarrhalis*.
- Azithromycin is now the preferred therapy for urethritis caused by *Chlamydia trachomatis*.
- It also has activity against *Mycobacterium avium-intracellulare* complex in patients with acquired immunodeficiency syndrome and disseminated infections.

Adverse effects

Gastrointestinal (GI) upset is common with the use of macrolides. It occurs in up to 21% of those who take erythromycin. Erythromycin and clarithromycin can cause arrhythmias by prolongation of the QT interval. Other adverse reactions include headache and tinnitus. Cholestatic jaundice with erythromycin.

Drug interaction

Erythromycin and clarithromycin inhibit the hepatic metabolism and causes accumulation of theophylline, warfarin and terfenadine. This can result in clinically important adverse effects.

Other protein synthesis inhibitors

Chloramphenicol (CAF)

Chloramphenicol has a broad spectrum of activity and penetrates tissues exceptionally well. It is bacteriostatic, but is extremely effective against streptococci, staphylococci, *H. influenzae*,

salmonellae and others. Uncommonly it causes aplastic anaemia and other serious adverse effects, so its use is largely confined to life-threatening disease (e.g. *H. influenzae* epiglottitis, meningitis, typhoid fever) and to topical use as eye drops.

New born infants cannot adequately metabolize CAF and thus, accumulation of free CAF cause the **gray baby syndrome**; Abdominal distention, vomiting, progressive cyanosis, irregular respiration, hypothermia, and vasomotor collapse.

Clindamycin

It is active against streptococci, staphylococci, bacteroides species and other anaerobes, both gram-positive and gram-negative.

Clinical uses:

- Clindamycin is used for the treatment of severe anaerobic infection caused by Bacteroides.
- Clindamycin plus primaquine is effective for moderate to moderately severe *Pneumocystis carinii* pneumonia.
- Is used in combination with pyrimethamine for AIDS-related toxoplasmosis of the brain.

11.3.3. Fluoroquinolones

Nalidixic acid is the first quinolone used for many years in treatment of urinary tract infections (UTIs). Introduction of the first fluorinated quinolone, norfloxacin, was rapidly followed by development of other members of this group, Ciprofloxacin, lomefloxacin, levofloxacin, ofloxacin, gatifloxacin, sparfloxacin, which has had wide clinical application.

Fluoroquinolones inhibit the enzyme DNA gyrase. This results in the inhibition of bacterial DNA synthesis.

Fluoroquinolones are formulated for oral, ophthalmic, and parenteral use. Oral absorption is good. Oral absorption is impaired by divalent cations like Ca^{2+} .

Antibacterial spectrum

- ❖ possess excellent activity against G-ve including Enterobacteriaceae, pseudomonas, haemophilus spp., Neisseria spp., Campylobacter

- ❖ Possess moderate to good activity against G+ve: methicillin susceptible strains of staph; streptococci & enterococci tend to be less susceptible
- ❖ Flouroquinolones also have activity against, Mycoplasma, chlamydia, legionella spp and Mycobacteria

Clinical uses

Ciprofloxacin is used for respiratory, urinary, gastro-intestinal and genital infections, septicaemia and meningococcal meningitis contacts. In addition to Pseudomonas, it is particularly active against infection with Salmonella, E. coli, Shigella, Campylobacter, Neisseria and Chlamydia.

Norfloxacin: is effective against both gram-negative (including P. aeruginosa) and gram-positive organisms in treating complicated and uncomplicated UTIs and prostatitis. It is not effective in systemic infections.

Adverse effects

In general, these agents are very well tolerated. Common adverse reactions are diarrhea, photosensitivity, dizziness, drowsiness, headache, nausea, and stomach upset. Cartilage deformities may occur in children and developing fetuses, so quinolones are contraindicated in children and pregnant women. Quinolones can also cause arrhythmias by prolongation of the QT interval.

11.3.4. Sulphonamides and trimethoprim

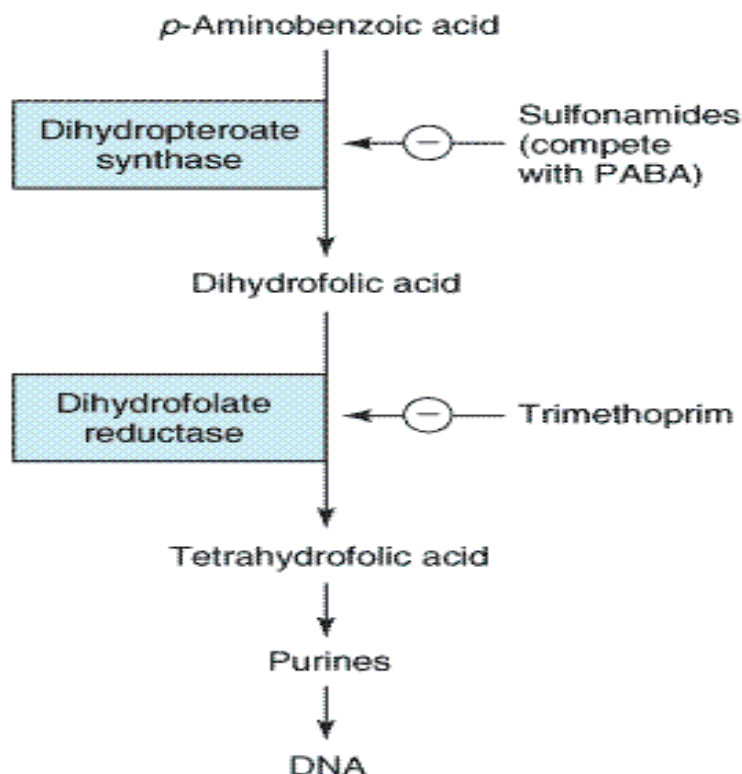
Sulfonamides were the first drugs available for systemic treatment of bacterial infections. There is now widespread resistance to Sulphonamides, and they have been largely replaced by more active and less toxic antibacterial agents. However, when cotrimoxazole was introduced in the mid-1970s, there was a renewed interest in the sulfonamides.

Sulfonamides can be divided into three major groups depending on their pharmacokinetics

- i. Oral, absorbable (systemic sulphonamides) E.g. Sulfisoxazole, sulfamethoxazole, Sulfadiazine, Sulfadoxine, etc...
- ii. Oral, nonabsorbable (those limited to GIT) E.g. Sulfasalazine
- iii. Topical E.g. sulfacetamide, mafenide acetate, etc...

Mechanism of action

Sulfonamides and trimethoprim are antifolate drugs. They interfere with the microbial synthesis of folic acid at separate steps in the biosynthetic pathway that ultimately leads to bacterial DNA synthesis inhibition.



Clinical Uses

- Infrequently used as single agents.
 - For infected burns (silver sulfadiazine given topically).
- Largely replaced by trimethoprim-sulfamethoxazole (Cotrimoxazole®).
- trimethoprim-sulfamethoxazole (Cotrimoxazole®) is used for
 - ✚ Urinary Tract Infections: - The combination appears to have special efficacy in chronic and recurrent infections of the urinary tract.
 - ✚ Bacterial Respiratory Tract Infections.
 - ✚ Gastrointestinal Infections: -Effective against sensitive strains of *Salmonella typhi* and other *Salmonella* spp. Acute diarrhea owing to sensitive strains of

enteropathogenic *E. coli* can be treated or prevented with either trimethoprim or trimethoprim plus sulfamethoxazole

Infection by *Pneumocystis jirovecii*

- Prophylaxis recommended for HIV-infected pts with fewer than 200 CD4 cells/ml

Adverse effects

Adverse reactions common with the use of sulfonamides

- ✓ hypersensitivity reactions
 - Mild reactions are common (rash, drug fever, photosensitivity).
 - Stevens –Johnson syndrome.
- ✓ Haematologic such as hemolytic anemia, granulocytopenia & thrombocytopenia
- ✓ Kernicterus in newborn
 - The drugs should NOT be given to infants under the age of 2 months, pregnant women near term or breastfeeding mothers
- ✓ Sulfonamides may promote the formation of crystals in the urine (crystalluria), especially if taken with acidic foods or beverages.

NB: - instruct the patient to take large volume of water while they are taking sulphonamide to prevent crystalluria.

11.3.5. Antimycobacterial Drugs

Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro. Their cell walls contain mycolic acids, which give the genus its name. *Mycobacterium tuberculosis* can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB). TB is the leading infectious cause of death worldwide, and over 2 billion people already have been infected. Increasing in frequency are diseases caused by non-tuberculosis mycobacteria (NTM). These species include *M. avium-intracellulare*, *M. chelonae*, *M. abscessus*, *M. kansasii*, and *M. fortuitum*. Finally, *M. leprae* causes leprosy.

M. tuberculosis is transmitted by inhalation of infective droplets coughed or sneezed into the air by patients with tuberculosis. *M. bovis* is transmitted by milk from diseased cows and first produces intestinal or tonsillar lesions.

Characteristics of mycobacteria that make the diseases chronic & necessitate prolonged treatment are:

- Mycobacteria grow slowly and may be dormant in the host for long periods
 - Many antibacterial do not penetrate mycobacterial cell walls
 - a portion of mycobacterium resides inside macrophages
 - Mycobacteria are agile in developing resistance to single chemotherapeutic agents
- ❖ Consequence $\Rightarrow$ effective therapy requires a prolonged course of multiple drugs which decreases Patient compliance, increases drug toxicity and drug interaction

TB treatment generally includes four first-line drugs which include isoniazid, rifampicin, pyrazinamide, ethambutol. Second-line drugs are typically less effective, more toxic, and less extensively studied including rifabutin, cycloserine, ethionamide, aminosalicylic acid, levofloxacin, capreomycin, amikacin, kanamycin. They are used for patients who cannot tolerate the first-line drugs or who are infected with resistant TB. Treatment for drug-susceptible TB lasts for at least 6 months, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.

Standard short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (the intensive phase), followed by isoniazid and rifampin for 4 months (the continuation phase). Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate persistent organisms and to prevent relapse.

One successful strategy for achieving better treatment completion rates is directly observed therapy, also known as DOT. Patients take their medications while being watched by a member of the health care team. DOT has been shown to decrease drug resistance and to improve cure rates. Most public health departments offer DOT services.

Isoniazid (INH)

It inhibits the synthesis of mycolic acid, an important constituent of the highly lipid cell wall of mycobacteria. The most active drug for the treatment of tuberculosis caused by susceptible strains. Is bacteriostatic for "resting" bacilli, but is bactericidal for rapidly dividing microorganisms. Remarkably selective for mycobacteria. Isoniazid is used as a single agent for treatment of latent tuberculosis, and for treatment of active TB in combination with others.

Adverse effects

Isoniazid may cause liver disease and nerve damage (neuropathy).

Note: isoniazide is often given with vitamin B6 (pyridoxine) to prevent neuropathy.

Rifampin

Has broader antimicrobial activity than isoniazid. It acts by blocking RNA synthesis by interacting with the β subunit of mycobacterial DNA-dependent RNA polymerase. It is also used to treat nasopharyngeal meningococcal carriers (it enters well into saliva, tears and nasal secretions), Legionnaires' disease and refractory deep seated staphylococcal infections (e.g. osteomyelitis). Rifampin also is highly active against *M. leprae*.

Adverse effects

- ✓ After a few hours influenza-like symptoms, flushing and rashes;
- ✓ Hepatotoxicity – hepatitis and cholestatic jaundice. It is important to monitor hepatic transaminases, particularly in patients at high risk of liver dysfunction (e.g. alcoholics). Serious liver damage is uncommon.
- ✓ Urine and tears become red-orange

NB: Inform the patient that the discolouration of body fluid (urine and tears) caused by rifampicin is harmless.

Drug interaction

Rifampicin markedly induces a wide range of hepatic microsomal CYP450 enzymes, thereby accelerating the metabolism of many commonly used drugs. Clinically important interactions associated with reduced concentration and therapeutic failure are common, and include: methadone, anticoagulants, some anticonvulsants, protease inhibitors, and contraceptives.

Ethambutol

Ethambutol is a synthetic, water-soluble, heat-stable compound. Nearly all strains of *M. tuberculosis* and *M. Kansasii* are sensitive. Ethambutol has no effect on other bacteria.

Mechanism of Action: Inhibits cell wall synthesis

Adverse effects

- ✚ The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. Prompt withdrawal of the drug may be followed by recovery. Testing of colour vision and visual fields should precede initiation of high-dose treatment, and the patient should be regularly assessed for visual disturbances;
- ✚ Rashes, pruritus and joint pains;
- ✚ Nausea and abdominal pain

Pyrazinamide

Pyrazinamide is a bactericidal drug which is well tolerated as oral therapy. Because of its ability to kill bacteria in the acid intracellular environment of a macrophage, it exerts its main effects in the first two to three months of therapy. **Pyrazinamide** is most active against slowly or intermittently metabolizing organisms, but is inactive against atypical mycobacteria.

Adverse effects

These include:

- ✚ Flushing, rash and photosensitivity
- ✚ Nausea, anorexia and vomiting
- ✚ Hyperuricemia and thus may cause gout
- ✚ Hepatitis (in approximately 5–15% of patients)

Table 11.1: common adverse effect of second line anti-TB drugs

Drug	Major adverse effects
Ethionamide and prothionamide	Hepatitis, gastro-intestinal and CNS disturbances, insomnia
PAS	Gastro-intestinal, rash, hepatitis
Capreomycin and Kanamycin	Similar to streptomycin
Cycloserine	Depression, fits and psychosis

11.3.6. Drugs Used in Leprosy

Leprosy can be treated effectively with dapsone and rifampin, adding clofazimine in multibacillary cases.

Dapsone

Dapsone is structurally related to the sulphonamides. It is bacteriostatic for *M. leprae*, and resistant strains may be encountered. Dapsone also is used in the treatment of pneumonia caused by *Pneumocystis jirovecii* in immunosuppressed patients. Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

Clofazimine

Clofazimine is bactericidal to *M. leprae*, and it has potentially useful activity against *M. tuberculosis*. Following oral absorption, the drug accumulates in tissues, allowing intermittent therapy but does not enter the CNS. Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance. Clofazimine has some anti-inflammatory and anti-immune activities.

11.4.Antifungal

Fungi, like mammalian cells but unlike bacteria, are eukaryotic and possess nuclei, mitochondria and cell membranes. However, their membranes contain distinctive sterols, ergosterol and lanosterol.

Fungal infections may be classified into two groups: **superficial mycoses** (of the skin) and **systemic mycoses**, which affect internal organs such as the lungs, digestive organs, and brain. Fungal infections are widespread in the population; they are generally associated with the skin or mucous membranes. Recently there is increase in local as well as systemic fungal infections. Reason for this is opportunistic infections

✚ Immuno-suppression due to

- Cancer chemotherapy
- AIDS
- Corticosteroid overuse

✚ Indiscriminate use of broad spectrum antibiotics

The antifungal agents fall into two major groups: drugs for systemic mycoses (i.e., systemic fungal infections) and drugs for superficial mycoses. A few drugs are used for both. Systemic infections occur much less frequently than superficial infections, but are much more dangerous.

- Superficial infections by Dermatophytes, Candida
- Deep infections are, Candidiasis, Aspergillosis, Coccidiomycosis, Histoplasmosis etc

Amphotericin B

Amphotericin B belongs to a group of drugs known as polyene antibiotics, so named because their structures contain a series of conjugated double bonds. Nystatin, another antifungal drug, is in the same family.

Key feature of Amphotericin B

- Wide spectrum of antifungal activity, fungicidal; makes 'pores' in fungal membranes.
- Available for topical (nystatin and amphotericin) treatment of common mucocutaneous fungal infections.

- Amphotericin is used intravenously for deep-seated and severe fungal infections (e.g. Aspergillus or histoplasmosis).
- Intravenous amphotericin is toxic, causing fever, chills, hypotension during infusion, nephrotoxicity, electrolyte abnormalities and transient bone marrow suppression.
- Kidney damage is the most serious adverse effect of amphotericin B.
- Systemic toxicity (especially nephrotoxicity) of amphotericin is reduced by using the liposomal/ lipid/micellar formulations.
- Amphotericin combined with 5-flucytosine have synergistic effect and used in severe infections and immunosuppressed patients.

Azoles

- Are synthetic and broad antifungal spectrum antifungal agents
- Drugs include:
 - Imidazole (clotrimazole, econazole, fenticonazole, ketoconazole, miconazole, tioconazole) or
 - Triazole (itraconazole, voriconazole and fluconazole).

Mechanism of action of azoles

Imidazoles competitively inhibit lanosterol 14- α -demethylase (a fungal cytochrome-haem P450 enzyme), which is a major enzyme in the pathway that synthesizes ergosterol from squalene. This disrupts the acyl chains of fungal membrane phospholipids, increasing membrane fluidity and causing membrane leakage and dysfunction of membrane-bound enzymes.

Fluconazole

Fluconazole is an antifungal for both systemic and superficial mycoses.

Indications: - Fluconazole has been shown to be effective against meningitis, as well as oropharyngeal and systemic candidiasis, both of which are commonly seen in AIDS patients. Fluconazole is also used for vaginal candidiasis.

Adverse Effects: - The most common adverse effects of fluconazole include elevated liver enzymes, gastrointestinal complaints, headache, and skin rash.

Fluconazole is used cautiously in patients with renal impairment.

Drug Interactions: - Fluconazole administration may increase the effect of oral hypoglycemic and decreases the metabolism of phenytoin and warfarin.

Ketoconazole

Ketoconazole is an antifungal agent effective for the treatment of candidiasis, histoplasmosis, blastomycosis, and aspergillosis.

Indications: - Ketoconazole is used for severe systemic fungal infections, including candidiasis (e.g., oral thrush, candiduric), chronic mucocutaneous and pulmonary candidiasis. Topical forms are available for superficial mycoses.

Adverse Effects: - Ketoconazole is usually well-tolerated. In some cases, nausea, vomiting, dizziness, headache, abdominal pain, and pruritus have been reported. Most adverse effects are mild and transient. In rare cases, fatal hepatic necrosis may occur. Periodic hepatic function tests should be used to monitor for hepatic toxicity.

Key features of azoles antifungal

- ✓ Relatively wide spectrum of antifungal activity, fungistatic, but fungicidal with higher concentrations.
- ✓ Available as intravenous, oral and topical formulations.
- ✓ Can be used as therapy for superficial (e.g. Candida) and serious deep-seated (e.g. Cryptococcus) fungal infections.
- ✓ Fluconazole, itraconazole and voriconazole are currently much more widely used than ketoconazole.
- ✓ Azole-related common toxicities are gastro-intestinal upsets, rashes, hepatitis and CYP3A inhibition-related drug–drug interactions.

Griseofulvin

Griseofulvin is a drug that is deposited in the skin, and bound to keratin. It is an antifungal, antibiotic, and anti-infective agent.

Clinical uses

Griseofulvin is orally active, but its spectrum is limited to dermatophytes. It is concentrated in keratinized cells. It is given orally with meals (fatty meals enhance absorption of griseofulvin) and treatment is recommended for six weeks for skin infections and up to 12 months for nail infections.

Adverse effects

- ✚ Headaches and mental dullness or inattention
- ✚ Diarrhoea or nausea
- ✚ Rashes and photosensitivity

Terbinafine

Terbinafine is fungicidal. It distorts hyphae and stunt the growth of susceptible fungi by blocking an enzyme needed for the synthesis of ergosterol.

It may be administered orally to treat ringworm (Tinea pedis, T. cruris or T. corporis) or dermatophyte infections of the nails.

Orally administered terbinafine may produce nausea, vomiting, altered taste, headache, and tiredness. Topical application of terbinafine may produce burning, stinging, redness, itchiness, and drying of the skin.

11.5. Antiviral drugs

Viruses are intracellular parasites that take over the metabolic machinery of host cells and use it for their own survival and replication, often resulting in the destruction of the infected cells. Viral diseases are the most common causes of disease in humans. Viruses result in a wide variety of diseases ranging from the common cold and the “cold sore” of herpes immune simplex to several types of cancers and AIDS.

Antiviral therapy is more difficult than antibacterial therapy because viruses are intimately incorporated in host cells and the therapeutic targets are often similar to the equivalent enzymes/structures in human cells. To summarize these problems:

- ✚ Viral replication is intracellular, so drugs must penetrate cells in order to be effective.
- ✚ Viral replication takes the metabolic processes of host cells.

✚ Although viral replication begins almost immediately after the host cell has been penetrated, the clinical signs and symptoms of infection often appear after peak viral replication is over.

Several events in the viral life cycle may prove susceptible as drug targets:

- Viral attachment to host cell, penetration, and uncoating
- Viral enzymes:
 - DNA/RNA polymerases, etc
 - Reverse transcriptases, proteases, etc.
- Host expression of viral proteins
- Assembly of viral proteins
- Release of virus from cell surface membranes

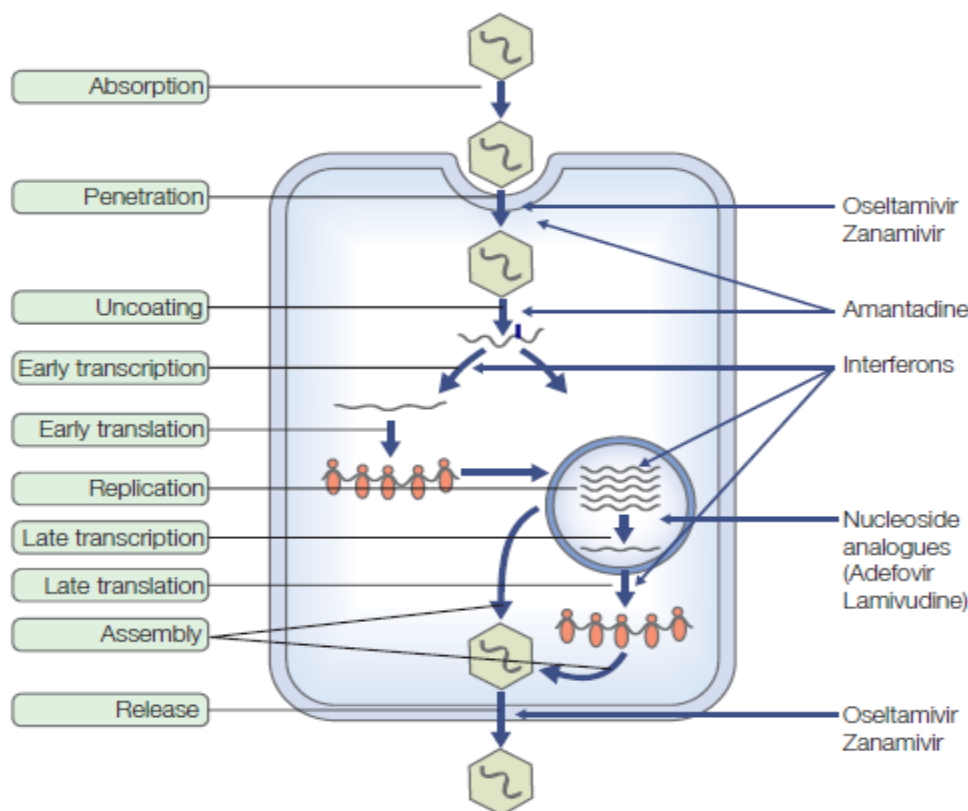


Figure 11.1: Virus life cycle and potential drug target

Antiviral Drugs

Antiviral drugs are used to treat viral infections by influencing viral replication. The majority of antivirals are active against only one virus, either DNA or RNA types. These viruses may include herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), hepatitis C virus and influenza A. The following antiviral drugs are a few examples.

Acyclovir

Acyclovir is a synthetic acyclic analog of guanosine with activity against various herpes viruses. Herpes viruses can infect neonates, children, and adults, causing a wide spectrum of diseases. Herpes simplex type 1 virus is responsible for systemic infections involving the liver and other organs, including the central nervous system, and localized infections that may involve the skin, eyes, and mouth. Other medically important herpes viruses include cytomegalovirus (CMV),

varicella (Chicken Pox), and varicella-zoster (shingles). **Acyclovir** is effective against herpes (simplex and zoster), but is much less active against cytomegalovirus. Acyclovir is available in capsules ranging from 200 to 800 mg and other dosage forms.

Mechanism of Action

Acyclovir is taken up selectively by cells that are infected with herpes viruses. Its activity depends upon conversion to the triphosphate where it becomes incorporated into viral DNA and inhibits viral replication.

Indications

Acyclovir is most effective against HSV-1 and HSV-2. IV acyclovir is used for HSV encephalitis, neonatal HSV, and life-threatening HSV and VZV infections in immunocompromised patients. Oral acyclovir is indicated for the treatment of primary and recurrent genital herpes. Acyclovir ophthalmic ointment is effective for herpes simplex keratitis.

Adverse Effects

Acyclovir may cause nausea, vomiting, and diarrhea. The drug can precipitate in the renal tubules with excessive dosages or when it is given by rapid infusion, which may cause acute renal failure. Other adverse effects of acyclovir include headache, drowsiness, fatigue, uncontrollable rhythmic shaking, confusion, and seizures.

Contraindications

Acyclovir is relatively contraindicated in pregnancy as it is an analogue of guanosine and so potentially teratogenic in the first trimester.

Other analogues

Famciclovir (prodrug of penciclovir) and valaciclovir (an acyclovir prodrug) have much greater bioavailability than acyclovir.

Table 11.2: List of other antiviral drugs

Drug name	Affected viruses	Adverse effect
Ganciclovir	cytomegalovirus	neutropenia and bone marrow suppression, GIT disturbance
Amantadine	prophylaxis and treatment of influenza A virus	dizziness, nervousness and headaches; • livedo reticularis.
Ribavirin	active against a number including hepatitis C	dose-related haemolytic anaemia and haematopoietic suppression; teratogenesis

Anti-retroviral drugs

HIV-AIDS (**acquired immunodeficiency syndrome**) is a global public health issue. HIV is the virus that causes AIDS. The virus attacks **CD4 T lymphocytes** and weakens the immune system. As the **CD4 count** declines the **viral load** increases, HIV-infected individuals are at increasing risk for developing opportunistic infections such as tuberculosis (TB), candidiasis, and CMV and other AIDS-defining conditions.

HIV life cycle

HIV, like other viruses, lacks the cellular machinery to reproduce itself. It incorporates its DNA into the DNA of the host cell; then, when the host cell tries to make new proteins, it accidentally makes new HIV as well. The steps in the HIV life cycle are briefly described here:

Step 1: Binding. The HIV binds to CD4 surface receptors.

Step 2: Fusion. The HIV is activated by proteins on the cell's surface, allowing the HIV envelope to fuse to the outside of the cell.

Step 3: Uncoating. The virus is uncoated, permitting the contents of the viral capsid (viral RNA and enzymes) to be released into the infected host cell.

Step 4: Reverse transcription. A viral enzyme called reverse transcriptase makes a DNA copy of the viral RNA.

Step 5: Integration. Viral DNA is incorporated into the host cellular DNA.

Step 6: Genome replication. The strands of viral DNA in the nucleus separate and mRNA provides instructions for making new virus (genome). This process is called transcription.

Step 7: Protein synthesis. The HIV mRNA genome acts as a template for synthesizing viral proteins needed to make a new virus in a process called translation.

Step 8: Protein cleavage and viral assembly. Protease is an enzyme that cuts the long chain of viral protein into smaller individual proteins. Some of the cleaved proteins become structural elements of new HIV and others become enzymes, such as reverse transcriptase. The new particles are assembled into new HIV.

Step 9: Virus release. New virus buds off from the host cell.

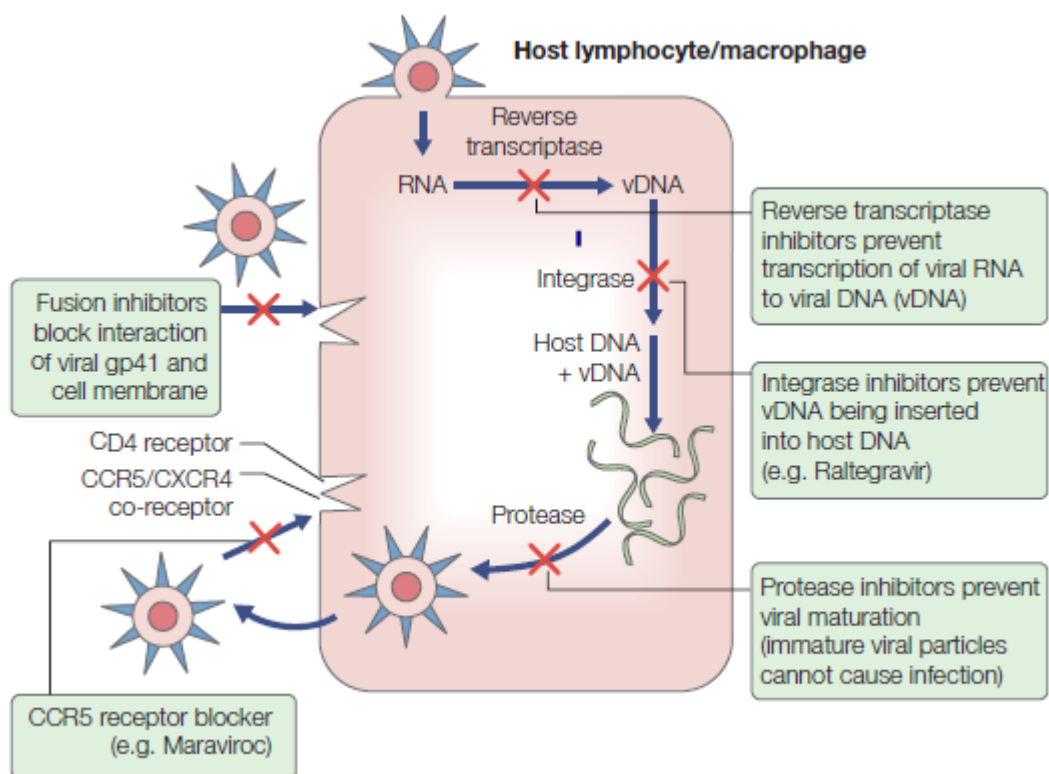


Figure 11.2: The life cycle of HIV and potential drug target

Anti-retroviral drugs are medicines that interfere with the replication of retroviruses. HIV is a retrovirus. Antiretroviral drugs are administered to reduce viral load, increase CD4 counts, delay the development of AIDS-related conditions and opportunistic infections, and improve survival. Antiretroviral drugs fall into six classes:

- ✚ Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- ✚ Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- ✚ Protease inhibitors (PIs)
- ✚ Fusion inhibitors
- ✚ Chemokine receptor antagonist, type 5
- ✚ HIV integrase strand inhibitor

Nucleoside reverse transcriptase inhibitors (NRTIs)

Drugs available in Ethiopia are zidovudine (ZDV), lamivudine (3-TC), Tenofovir (TDF), emtricitabine (FTC) and abacavir (ABC).

Key points of NRTIs

- ✚ Used in combinations to increase anti-HIV efficacy and reduce resistance
- ✚ Resistance develops slowly to NRTIs
- ✚ Lamivudine Well tolerated
- ✚ Abacavir is linked to a fatal hypersensitivity reaction that necessitates discontinuation of the drug
- ✚ Side effects associated with almost all NRTIs are headache, stomach upset, fatigue or insomnia, muscle ache, and diarrhea. Additionally, zidovudine may cause nail discoloration and anemia.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Agents in this group include efavirenz and nevirapine

Key points of NNRTIs

- ✚ Used in combination, because of synergy with NRTIs.
- ✚ Oral absorption is good, hepatic metabolism, short–intermediate half-lives.

- ✚ Adverse effects include gastro-intestinal disturbances, rashes and central nervous system disturbance with efavirenz
- ✚ Significant drug interactions
- ✚ Resistance develops quickly; not to be used as monotherapy.

HIV protease inhibitors (PIs)

Compounds in this class include amprenavir, ritonavir, indinavir, lopinavir, nelfinavir, atazanavir and Darunavir

Key points with PIs

- ✚ Used in combination, because of synergy with anti-HIV RT inhibitors and reduced resistance.
- ✚ They inhibit the HIV protease enzyme, and are the most potent and rapid blockers of HIV replication available.
- ✚ Oral absorption is variable, metabolized in liver
- ✚ Boosted PI therapy involves combinations such as lopinavir/ritonavir
- ✚ Side-effects: include gastrointestinal upsets, hyperglycaemia, fat redistribution and drug–drug interactions.
- ✚ HIV resistance to one agent usually means cross resistance to others in this class.

11.6.Anti-protozoal

Protozoa are single-celled parasitic organisms, many of which are motile. Most protozoa obtain their food from dead or decaying organic matter. Infection is spread through the ingestion of contaminated food or water, or through insect bites. Some protozoa are agents of disease, and some cause infections among the most serious known to humanity. Common infections caused by protozoa include amebiasis, malaria, toxoplasmosis, trypanosomiasis, trichomoniasis, and giardiasis.

11.6.1. Chemotherapy of Amebiasis

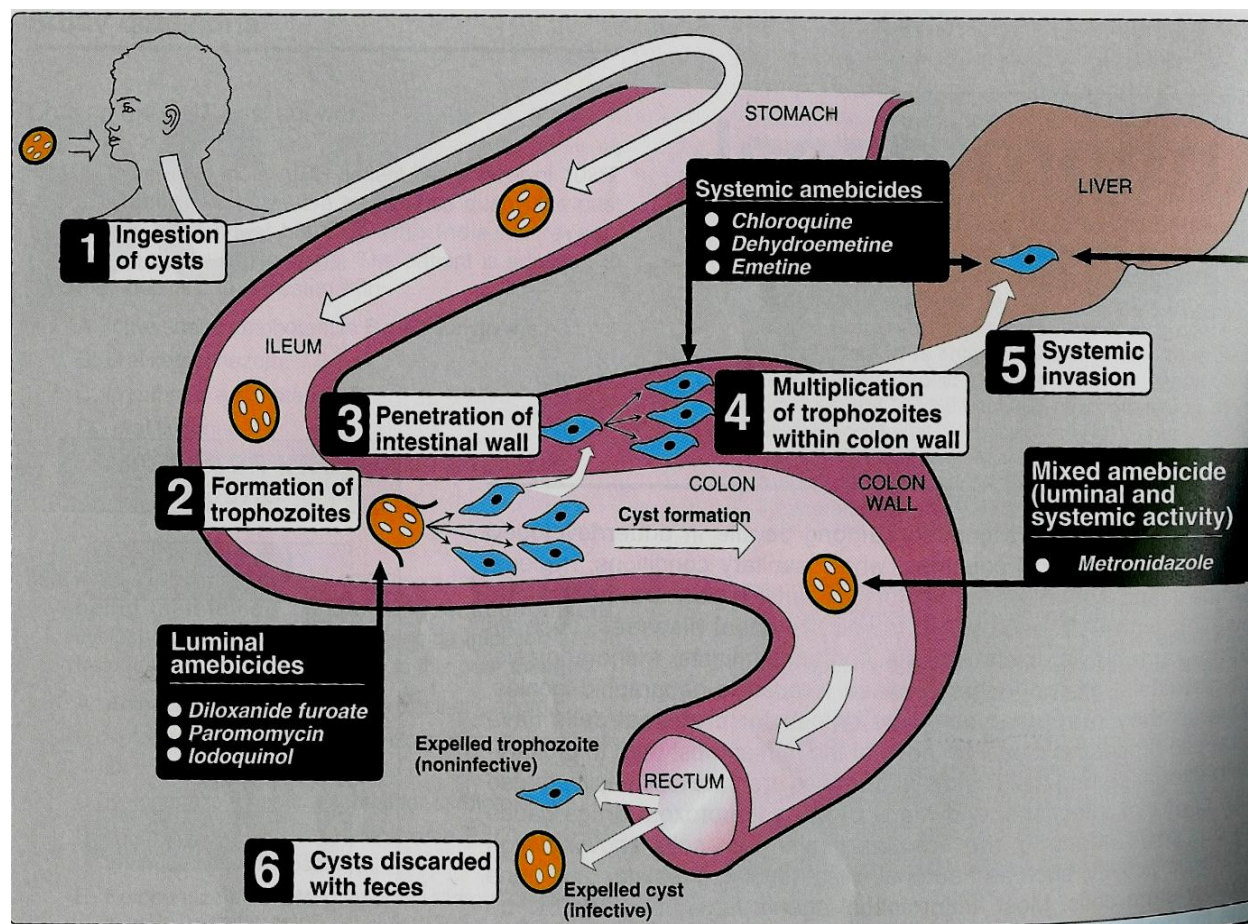
Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by *Entamoeba histolytica*. The disease can be acute or chronic, with patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. Therapy is aimed not only

at the acutely ill patient but also at those who are asymptomatic carriers, because dormant *E. histolytica* may cause future infections in the carrier and be a potential source of infection for others.

Cysts, ingested through feces-contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated. The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine or simply feed on intestinal bacteria. The trophozoites within the intestine are slowly carried toward the rectum, where they return to the cyst form and are excreted in feces. Large numbers of trophozoites within the colon wall can also lead to systemic invasion

The drugs important in the treatment of amebiasis, include metronidazole, Tinidazole and Diloxanide furoate.

- Metronidazole and tinidazole are active against both systemic and luminal forms of the disease
- Metronidazole has also antitrichomonal, and antibacterial action.
- Metronidazole is the treatment of choice for giardiasis.
- Diloxanide furoate is a luminal amebicide



Indications

Metronidazole is the drug of choice in amebic dysentery, giardiasis, and trichomoniasis. It is used in asymptomatic and symptomatic dysentery, which is a gastrointestinal disorder resulting from ulcerative inflammation of the colon caused chiefly by infection with *Entamoeba histolytica*. *Entamoeba*, *Giardia*, toxoplasma and trypanosomiasis. Metronidazole is also used in an acute intestinal amebiasis and amebic liver abscess. This agent commonly indicates for preoperative prophylaxis in surgery. IV metronidazole is used for the treatment of serious infections caused by susceptible anaerobic bacteria in intra-abdominal infections, skin infections, and septicemia.

Adverse Effects

Metronidazole causes nausea, vomiting, diarrhea, metallic taste or bitter taste, and, occasionally, neurologic reactions.

Note: Alcohol must be avoided while a patient is taking metronidazole; nausea and vomiting can occur if alcohol is ingested during therapy.

Tinidazole is a second generation nitroimidazole that is similar to metronidazole in spectrum of activity, absorption, adverse effects and drug interactions.

11.6.2. Antimalarial drugs

Malaria is a severe generalized infection caused by the bite of an anopheles mosquito that is infected with Plasmodium protozoa. The most important human parasite among the sporozoa is Plasmodium, which causes malaria. There are four different types of Plasmodium: *P. falciparum*, *P. malariae*, *P. vivax*, and *P. ovale*. Antimalarial drugs are selectively active during different phases of the protozoan life cycle (see figure below).

Key points

- ✚ Plasmodium falciparum infection has the highest mortality and causes cerebral malaria.
- ✚ *P. malariae*, *P. ovale* and *P. vivax* cause more benign disease.
- ✚ The hepatic forms of *P. ovale* and *P. vivax* cause relapses.
- ✚ Antimalarial drugs act at different stages of the malaria parasite's life cycle.
- ✚ Resistance, especially of *P. falciparum*, to chloroquine, and mefloquine is an increasing problem world-wide.

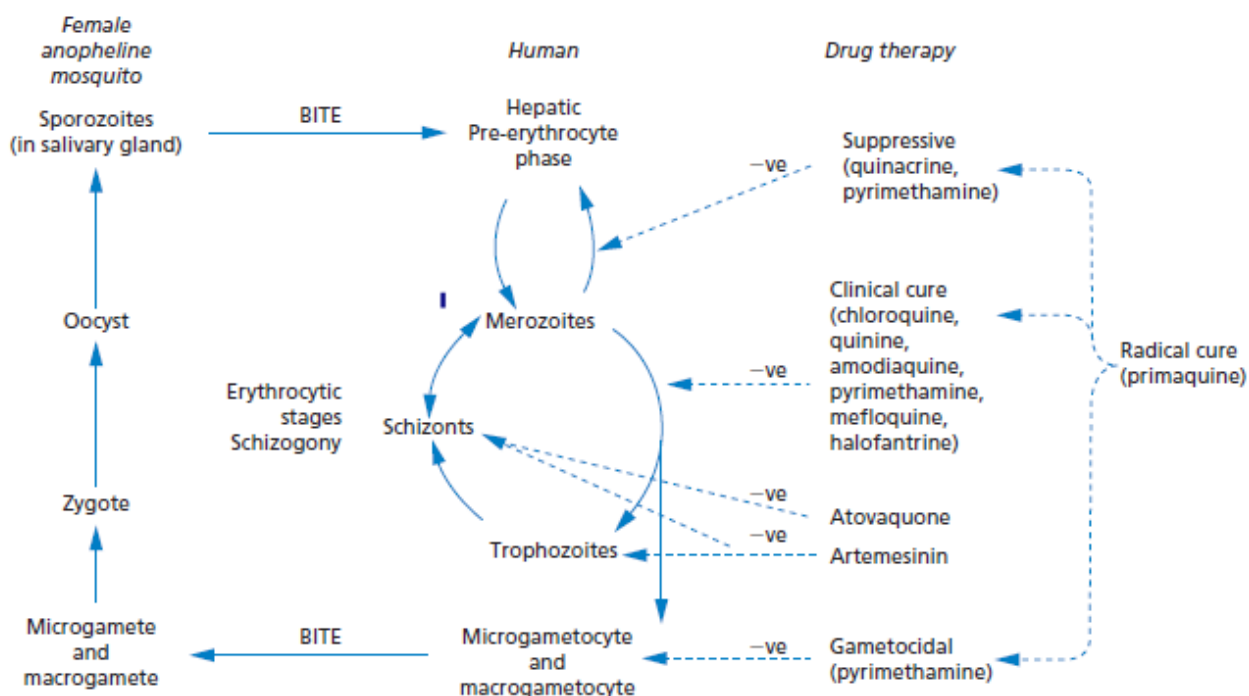


Figure 11.3: Malaria life cycle and antimalaria drug targets

Chloroquine

The erythrocyte stages of Plasmodium are sensitive to chloroquine. Chloroquine is still one of the most commonly used antimalarial drugs world-wide, but increasing resistance (especially *P. falciparum*) has reduced its efficacy.

It is used in

- ✚ Acute malaria
- ✚ Malaria prophylaxis
- ✚ Rheumatoid arthritis or systemic lupus erythematosus may be treated with chloroquine

Adverse Effects

Chloroquine and hydroxychloroquine can concentrate in the liver and must be used carefully in patients with liver diseases. They may cause visual disturbances, headache, and skin rash.

Drug interactions

Chloroquine and quinine are antagonistic and should not be used in combination.

Quinine

Quinine is the main alkaloid of cinchona bark. The mechanism of its antimalarial activity remains unclear, but may be similar to that of chloroquine.

Quinine sulphate (quinidine gluconate in the USA) is the drug of choice in the treatment of an acute attack of falciparum malaria where the parasite is known to be resistant to chloroquine.

Adverse effects

- ✚ Large therapeutic doses of **quinine** cause cinchonism
- ✚ Abdominal pain and diarrhoea;
- ✚ Rashes, fever, delirium, stimulation followed by depression of respiration, renal failure, haemolytic anaemia, thrombocytopenic purpura and hypoprothrombinaemia;
- ✚ Intravenous **quinine** can produce neurotoxicity such as tremor of the lips and limbs, delirium, fits and coma.
- ✚ Quinine stimulates insulin secretion and in therapeutic doses it can cause hypoglycemia

Artemisinin

Active principle of the Chinese medicinal herb *Artemisia annua*. Used as treatment of fevers in China for more than 2000 years.

Artenusate and artemether are semi-synthetic derivatives of artemisinin and are effective and well-tolerated antimalarial drugs. They should not be used as monotherapy or for prophylaxis because of the risk of resistance developing.

Available as coartem= Lumefantrine + artemether as Coartem

Adverse effects

- ✚ Nausea, vomiting and anorexia;
- ✚ Dizziness.

Mefloquine

Therapeutic use

- ✓ Chemoprophylaxis: nonimmune travelers
- ✓ Treatment: for malaria caused by chloroquine resistant & MDR *p. falciparum*

Adverse effects

- NVD; Abdominal pain, dizziness, dysphoria
- Higher doses cause
 - Neuropsychiatric toxicity [disorientation, seizure, encephalopathy]
 - Alter cardiac conduction, arrhythmias & bradycardia

Primaquine

- ✓ Active against hepatic stages of all human malarial parasite
- ✓ Gametocidal
- ✓ Reserved primarily for radical cure of vivax & ovale malarias

11.7. Anthelmintic Drugs

Helminths (worms) are multicellular organisms that infect very large numbers of humans and cause a broad range of diseases. Three major groups of helminths are the nematodes, trematode, and cestode that infect humans.

The main examples of worms that infect human are: -

Tapeworms: *Taenia saginata*, *Taenia solium*, *Hymenolepis nana* and *Diphyllobothrium latum*. Some 85 million people in Asia, Africa and parts of America harbour one or other of these

tapeworm species. The usual intermediate hosts of the two most common tapeworms (*Taenia saginata* and *Taenia solium*) are cattle and pigs, respectively. Humans become infected by eating raw or undercooked meat containing the larvae, which have encysted in the animals' muscle tissue.

Intestinal roundworms: *Ascaris lumbricoides* (common roundworm), *Enterobius vermicularis* (threadworm), *Trichuris trichiura* (whipworm), *Strongyloides stercoralis* (threadworm), *Necator americanus* and *Ankylostoma duodenale* (hookworms). Again, undercooked meat or contaminated food is an important cause of infection by roundworm, threadworm and whipworm, whereas hookworm is generally acquired when their larvae penetrate the skin.

Flukes: *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum*. These cause schistosomiasis (bilharzia). The adult worms of both sexes live and mate in the veins or venules of the gut wall or the bladder. The female lays eggs that pass into the bladder or gut and produce inflammation of these organs, resulting in haematuria in the former case and, occasionally, loss of blood in the faeces in the latter. The eggs hatch in water after discharge from the body and thus enter the secondary host—a particular species of snail. After a period of development in this host, free-swimming cercariae emerge. These are capable of infecting humans by penetration of the skin. About 200 million people are infected with one or other of the schistosomes.

Tissue roundworms: *Trichinella spiralis*, *Dracunculus medinensis* (guinea worm) and the filariae, which include *Wuchereria bancrofti*, *Loa loa*, *Onchocerca volvulus* and *Brugia malayi*. The adult filariae live in the lymphatics, connective tissues or mesentery of the host and produce live embryos or microfilariae, which find their way into the bloodstream. They may be ingested by mosquitoes or similar biting insects when they feed. After a period of development within this secondary host, the larvae pass to the mouthparts of the insect and are reinjected into humans. Major filarial diseases are caused by *Wuchereria* or *Brugia*, which cause obstruction of lymphatic vessels, producing elephantiasis. Other related diseases are onchocerciasis (in which the presence of microfilariae in the eye causes 'river blindness') and loiasis (in which the microfilariae cause inflammation in the skin and other tissues). *Trichinella spiralis* causes trichinosis; The worm may be up to a metre in length and has to be removed surgically or by slow mechanical winding of the worm on to a stick over a period of days.

Commonly used anti-helmentics include: mebendazole, albendazole, piperazine, praziquantel, levamisole, pyrantel pamoate and ivermectin

Mebendazole

A synthetic benzimidazole compound is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (*Trichuris trichiura*), pinworm (*Enterobius vermicularis*), hookworms (*Necator americanus* and *Ancylostoma duodenale*), and roundworm (*Ascariasis lumbricoides*).

Mebendazole is relatively free of toxic effects, although patients may complain of abdominal pain and diarrhea. It is, however, contraindicated in pregnant women, because it has been shown to be embryotoxic and teratogenic in experimental animals.

Albendazole

Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis (caused by *Taenia solium* larvae) and hydatid disease (caused by *Echinococcus granulosus*). The drug should not be given during pregnancy or to children under 2 years of age.

Pyrantel pamoate

Pyrantel pamoate, along with mebendazole, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms. Pyrantel pamoate is poorly absorbed orally and exerts its effects in the intestinal tract. Adverse effects are mild and include nausea, vomiting, and diarrhea.

Ivermectin

Ivermectin is the drug of choice for the treatment of onchocerciasis (river blindness) caused by *Onchocerca volvulus* and is a drug of first choice for cutaneous larva migrans and strongyloides. The drug is given orally. It does not cross the blood-brain barrier and, thus, has no pharmacologic effects in the CNS. However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable and CNS effects might be expected. Ivermectin is also contraindicated in pregnancy. The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, and hypotension).

Praziquantel

Trematode infections are generally treated with praziquantel. This drug is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis. Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite. Common adverse effects include drowsiness, dizziness, malaise, and anorexia, as well as gastrointestinal upsets. The drug is not recommended for pregnant women or nursing mothers.

Levamisole

It is effective in infections with the common round-worm as well as hook worm

MOA: It has a nicotine-like action, stimulating and subsequently blocking the neuromuscular junctions. The paralyzed worms are then expelled in the faeces. Ova are not killed.

Side effects: They include gastrointestinal disturbances, Dizziness and skin eruptions. High dose encephalopathy

Niclosamide

Used for treatment of Treatment of most forms of tape worms. It is poorly absorbed from gut & excreted in urine. Given in the morning on empty stomach. Purgative is necessary to purge all dead segments& prevent liberation of ova.

Piperazine

Piperazine can be used to treat infections with the common roundworm (*Ascaris lumbricoides*) and the threadworm (*Enterobius vermicularis*). When used to treat roundworm, piperazine is effective in a single dose. For threadworm, a longer course (7 days) at lower dosage is necessary

Side effects are uncommon, but gastrointestinal disturbances, urticaria and bronchospasm occur occasionally, and some patients experience dizziness, paraesthesias, vertigo and incoordination. The drug should not be given to pregnant patients or to those with compromised renal or hepatic function.

11.8. Anticancer drugs

Cancer is a disease that occurs when the normal cell renewal process fails. When old cells fail to die and new cells form more rapidly than needed, the cells may accumulate and form a mass called a **neoplasm** or **tumor**. Tumors are caused by abnormal cell division.

Risk Factors for Cancer

- ✚ Environmental pollutants, Tobacco
- ✚ Ionizing radiation such as Sunlight and tanning salons (UV light)
- ✚ Carcinogenic chemicals (e.g., benzene)
- ✚ Viruses (e.g., HPV, EBV)
- ✚ Hormone therapy
- ✚ Family history

Anticancer drugs

- alkylating agents (Cyclophosphamide, Ifosfamide, Chlorambucil) and related compounds, which act by forming covalent bonds with DNA and thus impeding replication
- antimetabolites, (Fludarabine, Hydroxyurea, Gemcitabine, Methotrexate, 6-Mercaptopurine), which block or subvert one or more of the metabolic pathways involved in DNA synthesis
- cytotoxic antibiotics, doxorubicin, idarubicin, daunorubicin i.e. substances of microbial origin that prevent mammalian cell division
- plant derivatives (vincristine, vinblastine and vindesine, Paclitaxel) -most of these specifically affect microtubule function and hence the formation of the mitotic spindle.
- Hormones, (tamoxifen) of which the most important are steroids, namely glucocorticoids, oestrogens and androgens, as well as drugs that suppress hormone secretion or antagonise hormone action.
- Miscellaneous agents that do not fit into the above categories. This group includes a number of recently developed drugs designed to affect specific tumour-related targets.

Adverse effects of cytotoxic chemotherapy

- Immediate effects

- nausea and vomiting (e.g. cisplatin, cyclophosphamide);
- drug extravasation (e.g. vinca alkaloids, anthracyclines, e.g. doxorubicin).
- Delayed effects
 - bone marrow suppression – all drugs;
 - alopecia; infection
 - drug-specific organ toxicities (e.g. skin and pulmonary – bleomycin; cardiotoxicity – doxorubicin);
 - psychiatric-cognitive morbidity;
 - teratogenesis.
- Late effects
 - gonadal failure/dysfunction;
 - leukaemogenesis/myelodysplasia;
 - development of secondary cancer.

Practice exercise I: Match the antibiotic class in List A with their respective clinical uses in List B (NB. more than one answer is possible).

List A	List B
1. Anti-bacterial agent	A. Lamivudine
2. Anti-retroviral agent	B. Metronidazole
3. Anti-cytomegalovirus	C. Rifampicin
4. Anti-malarial agent	D. Amoxicillin
5. Anti-fungal	E. Albendazole
6. Anti-helminthic agent	F. Amantadine
7. Antimycobacterial drugs	G. Lumefantrine + artemether
8. Anti- Leprosy drug	H. Ketoconazole
9. Anti-Amebiasis	I. Dapsone

10. Anti- influenza A virus	J. Acyclovir
	K. Efavirenz
	L. Metronidazole
	M. Chloroquine
	N. Griseofulvin
	O. Isoniazid
	P. Ciprofloxacin

Practice exercise II. Choose the best answer from the given options for the following questions.

- Which of the following statements concerning the use of antibiotics is the **LEAST** valid?
 - bactericidal agents should be selected for immunocompromised patients
 - initial therapy should employ agent(s) that provide broad coverage
 - definitive therapy should employ broad, rather than narrow spectrum agents
 - empirical therapy of fevers of unknown origin should be avoided
 - prophylactic therapy should be directed toward specific infectious agents
- Which of the following drugs is the **LEAST** likely to cause hemolysis in individuals deficient in glucose-6-PO4 dehydrogenase?
 - Sulfamethoxazole
 - Dapsone
 - Primaquine
 - Ciprofloxacin
- Clavulanic acid is combined with amoxicillin because:
 - It kills bacteria that are not killed by-amoxicillin
 - It reduces renal clearance of amoxicillin
 - It counteracts the adverse effects of amoxicillin
 - It inhibits beta lactamases that destroy amoxicillin

4. An 8-year-old child presented with brownish **discoloured and deformed anterior teeth**. History of having received an antibiotic about 4 years earlier was obtained. Which antibiotic could be responsible for the condition?

A. Chloramphenicol	C. Erythromycin
B. Tetracycline	D. Gentamicin
5. All of following are aminoglycosides, **EXCEPT**:

A. Gentamycin	C. Clindamycin
B. Streptomycin	D. Neomycin
6. What is the **most important reason** for restricted clinical use of chloramphenicol?
 - a. Its narrow spectrum of activity
 - b. Emergence of chloramphenicol resistance
 - c. Its potential to cause bone marrow depression
 - d. Its potential to cause superinfections
7. Cotrimoxazole is combination of
 - a. trimethprim and sulfamethoxazole
 - b. pyrimethamine and sulfadoxine
 - c. pyrimethamine and sulfadiazine
 - d. trimethoprim and sulfadoxine
8. Tetracyclines are avoided in pregnancy because they can
 - a. Cause abortions
 - b. Cause excessive postpartum hemorrhage
 - c. Affect the bones and teeth of the fetus
 - d. Cause excessive vomiting in the mother
9. The most serious adverse effects of aminoglycosides are:
 - a. Constipation and abdominal pain
 - b. Migraine headaches and phlebitis
 - c. Muscle weakness and dry mouth
 - d. Ototoxicity and nephrotoxicity
10. Which of the following is **not** a first line antitubercular drug?

A. Ciprofloxacin	C. Pyrazinamide
B. Streptomycin	D. Ethambutol

11. Pyridoxine given to a patient of tuberculosis prevents

- a. INH induced peripheral neuritis
- b. Rifampicin induced hepatotoxicity
- c. Ethambutol induced visual defects
- d. Streptomycin induced nephrotoxicity

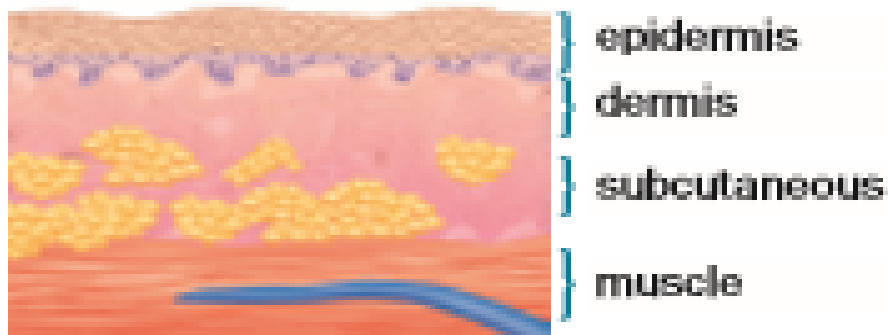
12. Drugs Used in Dermatological Disorders

Dear trainees, at the end of this chapter, you will be able to:

- + List and categorize medications used to treat common skin disorders
- + Describe the indication and common adverse effects of medications used for skin disorders

12.1. Introduction to the skin

The skin is the largest organ in the human body. It is the body's first line of defense, acting as a barrier against disease and physical hazards. It also helps control body temperature by releasing heat through sweat or by constricting blood vessels to act as insulation.



The skin consists of two main compartments; the epidermis and the underlying dermis. The epidermis has blood or nerves and is constantly discarding dead cells. It consists of multiple layers of keratinocytes, melanocytes, and Langerhans cells.

Table 12.1: Main functions of each cell in the epidermis

Cell types	Main functions
Keratinocytes	Produce keratin as a protective barrier
Langerhan's cells	Present antigens and activate T-lymphocytes for immune protection
Melanocytes	Produces melanin, which gives pigment to the skin
Merkel cells	Contain specialized nerve endings for sensation

The dermis contains capillaries nerves, and also sebaceous glands and sweat glands. It provides a base for the epidermis and contains fibroblasts that elaborate proteins, such as collagens and elastin, which are crucial for the skin's structural integrity.

12.2. Skin disinfectants

- applied topically to living tissue
- destroy micro-organisms or inhibit their reproduction or metabolic activities
- minimize potential for infection are of limited value - only adjuncts to removal of dirt and organic matter.
- drugs: ethyl alcohol, Hydrogen Peroxide, Chlorhexidine Gluconate + cetirizine, Povidone-Iodine, Iodine, Potassium Permanganate

12.3. Topical anti-bacterials

- Common bacterial skin diseases
 - Staphylococcal infections of the skin such as impetigo, folliculitis, and furunculi and
 - streptococcal infections such as cellulitis are very common
- **Silver sulfadiazine**
 - is bactericidal against both Gram-positive and Gram-negative organisms used for treatment of infected burns.
- **Nitrofurazone**

- Indications: as an adjunctive therapy for second and third degree burns when resistance to other agents is a real or potential problem.
- **Sodium Fusidate**
 - Indications: staphylococcal skin infections and treatment of primary and secondary skin infections caused by susceptible organisms
 - **Side effects: rarely hypersensitivity reactions**
 - Contraindications: hypersensitive to fusidates and hypersensitivity to fusidic acid or any component of the formulation

Table 12.2: Clinical uses of selected topical antibacterial drugs

Drug	Clinical use
Clindamycin	Acne vulgaris
Erythromycin	Acne Vulgaris
Metronidazole	Acne rosacea
Bacitracin	Superfacial infection (gram positive bacteria)
Polymyxin B	Superfacial infection (gram negative bacteria)
Neomycin	Superfacial infection (mainly gram-negative bacteria)

12.4. Ectoparasiticides (Drugs used to treat scabies and lice)

- **Available drugs**
 - **crotamiton cream 10%, sulfur ointment 5%, 10%, permethrin cream 5%, Benzyl Benzoate lotion 25%**
- **Crotamiton**
 - is a scabicide with some antipruritic properties
 - Application to acutely inflamed skin or to the eyes or mucous membranes should be avoided
- **Permethrin**
 - is toxic to *Pediculus humanus*, *Pthirus pubis*, and *Sarcoptes scabiei*
 - is used for pediculosis and scabies

- in cases of pediculosis, it is applied for 10 minutes and then rinsed off with warm water.
- for the treatment of scabies, a single application of 5% cream (Elimite) is applied to the body from the neck down, left on for 8–14 hours, and then washed off
- Adverse reactions to permethrin include transient burning, stinging, and pruritus
- **Sulfur**
 - has a long history of use as a scabicide.
 - it is nonirritating, but it has an unpleasant odor, is staining, and is thus disagreeable to use.
 - It has been replaced by more aesthetic and effective scabicides in recent years
- **Benzyl Benzoate**
 - Indications: scabies; head, body and pubic lice.
 - Side effects
 - slight local irritation, transient burning sensation, occasionally rashes.
 - Frequent use causes contact dermatitis
 - Cautions
 - avoid contact with face, eyes, mucous membranes and urethral meatus.
 - Do not apply to inflamed skin or weeping surfaces;
 - not recommended for children; breastfeeding (withhold during treatment).

12.5. Topical antifungals

Mycoses is classified as superficial, deep or systemic. Dermatophytosis (tinea) infections most common involve skin, hair and nails caused by Epidermophyton, Trichophyton, and Microsporum.

- Resistant fungi or involvement of hair or nails requires prolonged oral griseofulvin or ketoconazole.
- mild to moderate tinea
 - miconazole (14-28 days) or tioconazole - tolnaftate, compound undecylenic acid.
 - also, salicylic acid effective due to keratolytic effect
 - topical clotrimazole, econazole, miconazole, sulconazole or ciclopirox
 - infections of palms, soles, and fingernails may require oral griseofulvin

- Tinea versicolor
 - selenium sulfide suspension - 15-30 min. daily for 7 to 14 days
 - sodium thiosulfate 25% with salicylic acid 1% also effective
 - zinc pyrithione shampoo
- Superficial Candidiasis
 - responds to topical preparations of polyene antibiotics (amphotericin B, nystatin)
 - imidazoles (clotrimazole, econazole, miconazole)

Table 12.3: Topical Antifungal Drugs and Courses of Treatment for Tinea Pedis

Drug	Frequency of application	Duration (weeks)
Clotrimazole	bid	4
Econazole	qd	4
Ketoconazole	qd	6
Miconazole	bid	4
Oxiconazole	qd	4
Terbinafine	bid	1-4
Tolnaftate	bid	4

- Most other local ringworm infections can be treated adequately with topical antifungal preparations.
 - Benzoic acid and methylrosanilinium chloride (**genetian violet**) solution are inexpensive and effective fungistatic compounds for the treatment of ringworm infections.
- Minor skin lesions due to ringworm can be cleared with repeated applications of compound benzoic acid ointment (**Whitfield ointment**), which combines the fungistatic action of benzoic acid with the keratolytic action of salicylic acid.

12.6. Topical antiviral drugs

Acyclovir Ointment, 5%

- Indications
 - treatment of mucocutaneous herpes simplex infections, herpes labialis, for serious skin and mucosal (including genital) herpetic infections.
- Cautions
 - indiscriminate use of topical acyclovir may result in the emergence of resistance. It has no role in the treatment of herpes zoster.
- Side effects
 - mild pain, burning or stinging often occurs when applied to ulcerated lesions. Erythema, itch, mild dryness and skin hypersensitivity rashes occur.

12.7. Topical Anti-Inflammatories**Topical corticosteroids**

- are the most widely prescribed drugs for skin diseases
- have anti-inflammatory and immunosuppressive effects
- are most useful in inflammatory dermatoses, such as **eczematous dermatitis** and psoriasis
- they may also be helpful in other skin diseases that have a prominent inflammatory component, such as autoimmune blistering diseases (e.g., bullous pemphigoid and pemphigus vulgaris) and lupus erythematosus.
- Many preparations of topical corticosteroid are available including
 - Betamethasone dipropionate cream, ointment 0.025%, 0.05%
 - Clobetasol propionate cream, ointment 0.05%
 - Betamethasone valerate ointment 0.1%
 - Triamcinolone acetonide ointment 0.1%, cream 0.5%
 - Desoximetasone cream 0.05%
 - Dexamethasone Sodium Phosphate Cream, 0.1%
 - Hydrocortisone acetate ointment 1%, cream 0.1%
 - Betamethasone dipropionate lotion 0.05%

- Anti-Infective/Anti-Inflammatory Combinations
 - Clioquinol + Hydrocortisone Cream, 3% + 0.5% or 1% Ointment, 3% + 0.5% or 1%
 - Isoconazole + Diflucortolone valerate Cream, Ointment, 1% + 0.1%
 - Clotrimazole + Hydrocortisone Cream, Ointment 1% + 1%

12.8. Keratolytics

- Drugs that are used to treat hyperkeratosis, a thickening of the stratum corneum, are called keratolytics
- are especially useful for treatment of **corns and calluses, warts, palmoplantar keratodermas, ichthyoses, and psoriasis**
- The precise mechanisms by which these agents treat hyperkeratosis are not known.
 - Presumably, a common property is the ability to denature keratin, the major structural protein of the epidermis.
- Examples of these agents are **salicylic acid, urea, lactic acid, and colloidal or precipitated sulfur**.
- **Salicylic acid**
 - has been extensively used in dermatologic therapy as a keratolytic agent
 - is keratolytic in concentrations of 3–6%.
 - In concentrations greater than 6%, it can be destructive to tissues
 - Urticarial, anaphylactic, and erythema multiforme reactions may occur in patients who are allergic to salicylates.
 - Topical use may be associated with local irritation, acute inflammation, and even ulceration with the use of high concentrations of salicylic acid
 - preparations available: Ointment, 2%, 5%, 10%

12.9. Acne preparations

Retinoic Acid

- Retinoic acid, also known as tretinoin or all-trans-retinoic acid, is the acid form of vitamin A.
- It is an effective topical treatment for acne vulgaris
- The most common adverse effects of topical retinoic acid are erythema and dryness that occur in the first few weeks of use
- available preparation: Cream, 0.025% Gel, 0.01%, 0.025% Lotion, 0.025%, 0.05% Ointment, 0.05%

Benzoyl Peroxide

- Benzoyl peroxide is an effective topical agent in the treatment of acne vulgaris
- It is converted in the skin to benzoic acid; clearance of absorbed drug is rapid, and no systemic toxicity has been observed.
- The major toxicities are irritation and contact allergy
- available preparations: Gel, 2.5%, 5%, 10% Solution, 2.5%, 5%, 10%

12.10. Sunscreens

- Sunscreens absorb ultraviolet radiation before it can be absorbed in the skin.
- They are recommended to protect the skin from the major toxicities of sun exposure: sunburn and skin cancer.
- Most available agents primarily absorb UVB, although newer preparations also provide protection against UVA.
- Physical sunscreens (which are generally opaque, **like titanium dioxide and zinc oxide**) block all ultraviolet radiation.

Practice exercise: choose the best answer for the following questions

1. A topical antibacterial drug used for treatment of acne

- a. Acyclovir b. clindamycin c. Clobetasol propionate
- 2. Which one of the following drugs is keratolytic drug?
 - a. Salicylic acid b. retinoic acid c. zinc oxide
- 3. Indicate a drug used for treatment of scabies and lice?
 - a. Crotamiton b. sulfur c. benzyl benzoate d. all

13. Vaccines and Biologic Products

Dear trainees, at the end of this unit, you will be able to:

- ✚ Describe the indications, side effects, routes of administration and storage conditions of common vaccines and immunological preparations.

13.1. Immunoglobulins

- Immunoglobulins are **preparations** containing antibodies against infectious micro-organisms
- They are prepared usually from human plasma or serum.
- They are used for passive immunization, thus conferring immediate protection against some infectious diseases.
- **Side effects:**
 - pain and tenderness at the site of intramuscular injection;
 - hypersensitivity reactions (anaphylactic reactions)
 - systemic reactions with fever, chills, facial flushing, headache, and nausea (I.V.)
- An interval of 3 months should be allowed between the use of live vaccines and the prior administration of immunoglobulins

13.2. Antisera

- Antisera (immunosera) are sterile preparations containing immunoglobulins obtained from the serum of immunized animals by purification.
- Antisera have the specific power of neutralizing venoms or bacterial toxins, or combining with the bacterium, virus, or other antigen used for their preparation.
- Sensitivity testing should be performed before the administration of antisera

13.3. Vaccines

- Vaccines are preparations of antigenic materials which are administered with the object of inducing in the recipient active immunity to specific bacteria or viruses.
- They may contain living or killed microorganisms, bacterial toxoids, or antigenic material from particular parts of the bacterium, rickettsia or virus.
- The term vaccination and immunization are often used synonymously and interchangeably.
- Vaccination is strictly only the administration of a vaccine whereas immunization results in the demonstrable presence of protective levels of antibodies confirmed usually by serological testing.
- Vaccination should be postponed in patients suffering from any acute illness although minor infections without fever or systemic upset are not regarded as contraindications.
- Before injection of a vaccine any alcohol or disinfectant used for cleansing the skin should be allowed to evaporate otherwise inactivation of live vaccines may occur.
- Vaccines are **contraindicated** in those:
 - Who have a confirmed anaphylactic reaction to a preceding dose of a vaccine containing the same antigens or vaccine component (such as antibacterial in viral vaccines).
 - Hypersensitivity to egg especially for (influenza vaccine for prepared in hens' eggs), tick-borne encephalitis vaccine, and yellow fever vaccine.
 - Who are immune suppressed (Live vaccines);
 - Pregnant.
- **Immune response to vaccines** may be reduced in immune-suppressed patients and there is also a risk of generalized infection with live vaccines.
- Severely immune-suppressed patients should not be given live vaccines (including those with severe primary immunodeficiency).
- High doses of corticosteroids or other immunosuppressive drugs and those being treated for malignant conditions with chemotherapy or generalized radiotherapy can face reduction of immunity. So they have to see specialist advice.
- **Live vaccines** should not be administered routinely to **pregnant** women

- But, where there is a significant risk of exposure to disease (e.g. to yellow fever), the need for vaccination usually outweighs any possible risk to the fetus.
- Termination of pregnancy following unplanned immunisation is not recommended.
- **Inactivated vaccines** can be provided for pregnant women.
- There is no evidence of risk from vaccinating women who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids. Therefore, they **can be indicated** for women who are breast-feeding can be **vaccinated**
- Generally, vaccines and related biologic products constitute an important group of agents that bridge the disciplines of microbiology, infectious diseases, immunology, and immunopharmacology.
- A list of the most important preparations is provided here.

Side effects of vaccine:

- pain, inflammation, and lymphangitis (lymph inflammation)
- nausea, vomiting, fever, headache, irritability, loss of appetite, fatigue,
- influenza-like symptoms
- Hypersensitivity reactions, such as bronchospasm, angioedema, urticaria, and anaphylaxis, are very rare but can be fatal

Route of administration:

- Vaccines should not be given intravenously.
- Most vaccines are given by the intramuscular route except for bleeding disorders such as hemophilia or thrombocytopenia
- Some vaccines are given by others routes—the intradermal route for BCG vaccine, and the oral route for cholera, live poliomyelitis, rotavirus, and live typhoid vaccines.

Storage and use:

- Many vaccines and immunoglobulins need to be stored at 2–8°C and not allowed to freeze.
- Protect from from light
- Reconstituted vaccines and opened multi-dose vials must be used within the period recommended in the product literature.

- Vaccines which are liquid suspensions or are reconstituted before use should be adequately mixed to ensure uniformity of the material to be injected.

Table 13.1: Common Vaccines and Immunological Preparations Available

Vaccine	Indication	Dosages
Anti-Rho(D) Immune Globulin	➤ To prevent a rhesus (Rh) negative mother actively forming antibodies to fetal rhesus positive	Injection, 2ml in vial, 120mcg, 300mcg
BCG Vaccine	➤ Active immunization against tuberculosis.	Injection, 500,000 organisms /ml in 0.05ml and 0.1ml
Diphtheria Antitoxin	➤ for passive immunization in suspected cases of diphtheria and should be given without waiting for bacteriological confirmation of the infection.	Injection, 2000 units/ml in 5ml
Diphtherial and Tetanus Toxoid	➤ Active immunity against diphtheria and tetanus when pertussis vaccine is contraindicated. ➤ tetanus prophylaxis in wound management	Injection, 0.5 ml
Diphtheria and Tetanus Toxoid, Pertussis Vaccine	➤ active immunization against diphtheria, tetanus, and pertussis from age 6 weeks through 7 years of birth ➤ not used for children > 7 years of age	injection, 0.5ml
Hepatitis B Vaccine, (inactivated, Recombinant Yeast DNA)	➤ for active immunization against hepatitis B infections in persons at high risk of contracting the disease	Injection, 16.5% in 2ml, 10ml, Injection, 0.5ml
Human Anti-Rabies Immunoglobulin	➤ Passive immunization either post-exposure or in suspected exposure to rabies in high-risk countries in unimagined individuals	Injection, 150 IU/ml in 2ml
Measles Virus Vaccine Live Attenuated	➤ active immunization against measles	Injection, 0.5ml
Pentavalent (Diphtheria, Pertussis, Tetanus,	➤ Active immunization against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus Influenzae B at completion of 2, 4 and 6 months of age.	Injection, 0.5ml

Herophilus Influenzae B, and Hepatitis B) Vaccine		
Rabies (Human Diploid Cell) Vaccine	➤ for active immunization against rabies. ➤ for post exposure treatment to patient who have been bitten by rabid animals or animals suspected of being rabid ➤ for pre-exposure prophylaxis against rabies in persons at high risk of exposure to rabies vaccine.	Injection, 2.5IU/ml in 2ml
Rota Virus Vaccine	➤ immunization against gastro-enteritis caused by rotavirus	Oral solution, 2ml
Snake Venom Antiserum Polyvalent	➤ to prevent or minimize the effects of poisoning by these snakes ➤ polyvalent neutralizes absorbed venom of snakes venom	Inection, 10ml
Tetanus Antitoxin, Equine	➤ Indicated for temporary passive immunization against tetanus and ➤ To prevent tetanus infection that arise from the toxins produced by Clostridium tetani.	Injection, 1500 Units, 3000Units, 20,000Units
Tetanus Toxoid	➤ active immunization against tetanus and neonatal tetanus; ➤ Wound management (clean wounds).	Injection, 0.5ml, 1ml
Yellow fever Vaccine	➤ Active immunization against yellow fever.	Injection, 50 Doses

14. Nutritional products

Dear trainees, at the end of this chapter you will be able to:

- 🚦 Identify common vitamins, electrolytes, nutritional supplements and minerals

14.1. Vitamins

Vitamins are nutrients that are essential for normal cellular function, but are required in much smaller quantities than the aliments (carbohydrates, fats and proteins). Vitamins are essential cofactors to or components of enzymes that are integral in intermediary metabolism and many other biochemical processes.

An abnormal condition resulting from excessive intake of toxic amounts of one or more vitamins, especially over a long period, is called hypervitaminosis. Hypovitaminosis may occur due to a deficiency of one or more vitamins.

Vitamins are divided into two categories:

- i. **Water soluble** – vitamin B complex (including vitamin B12, folate, thiamine, nicotinic acid, pantothenic acid and biotin), vitamin C
- ii. **Fat soluble** – vitamins A, D, E and K

Vitamin A (Retinoic acid)

Vitamin A (retinol) has essential roles in the development of vision, bone growth, the maintenance of epithelial tissue, the immunological process, and normal reproduction.

- Three forms: - retinol, retinal and retinoic acid
- Sources: - animal – retinol vegetable – provitamins (carotenes) which are converted to vitamin A in liver
- Normal Laboratory value: adult – 20-100 mcg/dl
- Causes of deficiency
 - inadequate dietary intake
 - Pregnancy Lactation
 - Mal-absorption syndrome and Hepato-biliary disease

- Manifestations of deficiency:
 - Xerophthalmia -involves xerosis (dryness) of eye,
 - night blindness (nyctalopia) progressing to total blindness,
 - Dry and rough skin with papules,
 - hyperkeratinisation,
 - Keratinization of bronchopulmonary epithelium,
 - increased susceptibility to infection

Uses

Tretinoin (all trans-retinoic acid) and isotretinoin (synthetic retinoid) are used in acne vulgaris and to facilitate healing of skin. For prophylaxis in children.

Adverse effects

Long-term ingestion of more than double the recommended daily intake of vitamin A can lead to toxicity and chronic hypervitaminosis.

- ✚ itching and dry skin;
- ✚ raised intracranial pressure irritability and headache;
- ✚ tender hyperostoses in the skull and long bones;
- ✚ hepatotoxicity;
- ✚ congenital abnormalities

Contraindications

Excess vitamin A during pregnancy causes birth defects. Therefore, pregnant women should not take vitamin A supplements,

Vitamin D

Vitamin D (calciferol) is another fat-soluble vitamin that is chemically related to steroids and essential for the normal formation of bones and teeth and for the absorption of calcium and phosphorus from the GI tract. Ultraviolet rays activate a form of cholesterol in an oil of the skin and convert it to a form of the vitamin, which is then absorbed. Deficiency of the vitamin results in rickets in children, the destruction of bony tissue, and osteoporosis.

Vitamin D is used for the prophylaxis and treatment of **rickets**, **osteomalacia**, and other hypocalcemic disorders (tetany) and hypoparathyroidism. Vitamin D₃ is the predominant form of vitamin D of animal origin. It is found in most fish liver oils, butter, bran, and egg yolks. It is formed in skin exposed to sunlight or ultraviolet rays.

Hypervitaminosis D produces a toxicity syndrome that may result in hypercalcemia, malabsorption (which can lead to constipation), kidney stones, and calcium deposits on bones. Vitamin D therapy is contraindicated in hypercalcemia, malabsorption syndrome, and renal dysfunction, or if an individual has evidence of vitamin D toxicity or abnormal sensitivity to the effects of vitamin D. Vitamin D₂ is also called ergocalciferol.

Vitamin E

Vitamin E (tocopherol) is a fat-soluble vitamin that is essential for normal reproduction, muscle development, and resistance of erythrocytes to **hemolysis**. It is an intracellular antioxidant and acts to maintain the stability of polyunsaturated fatty acids.

Deficiency of vitamin E is rare, but can lead to anemia in babies, especially if premature. In adults, erythrocytes may have a shortened lifespan, which may result in muscle degeneration of vascular system abnormalities and kidney damage.

Vitamin E is relatively non-toxic, and may cause problems only in the large-dosage range of about 300 mg per day (RDA is only 10 mg per day). At this range, interference with thyroid function and a prolonging of blood clotting time may occur. Sources of vitamin E include vegetable oils such as soybean, corn, cottonseed, and sun flower, as well as nuts, seeds, and wheat germ.

Vitamin K

Vitamin K is essential for the synthesis of prothrombin in the liver. The naturally occurring forms, also called quinones, are vitamin K₁ (phylloquinone), which occurs in green plants, and vitamin K₂ (menaquinone), which is formed as the result of bacterial action in the intestinal tract. Water-soluble forms of vitamins K₁ and K₂ are also available. The fat-soluble synthetic compound, **menadione (vitamin K₃)**, is about twice as potent biologically as the naturally occurring vitamins K₁ and K₂, on a weight basis.

Vitamin K is used for coagulation disorder and vitamin K deficiency.

It is given prophylactically to infants to prevent hemorrhagic disease of the newborn. Natural vitamin K is stored in the body and is not toxic

Vitamin B Complex

Vitamin B complex is a group of water-soluble vitamins that differ from each other structurally and in their biologic effects. Heat and prolonged cooking, especially cooking with water, can destroy B vitamins.

Vitamin B1 (thiamine) is a water-soluble component of the B vitamin complex that is essential for normal metabolism and the health of the cardiovascular and nervous systems. Thiamine plays a key role in the metabolic breakdown of carbohydrates. Rich sources of vitamin B1 are pork, organ meats, green leafy vegetables, legumes, sweet corn, egg yolks, corn meal, brown rice, yeast, and nuts. Deficiency of thiamine leads to the disease called beriberi, which has neurologic, cardiovascular, and GI symptoms. Thiamine toxicity can occur if very large doses are taken for long periods, and this can result in hepatotoxicity.

Alcohol is well-known for its ability to inhibit the absorption of thiamine and folic acid. Alcohol abuse is the most common cause of thiamine deficiency.

Vitamin B2. Vitamin B2 (riboflavin) is one of the heat-stable components of the B vitamin complex. It is essential for certain enzyme systems in the metabolism of fats and proteins. It is sensitive to light. It plays an important role in preventing some visual disorders, especially cataracts.

Vitamin B3. Vitamin B3 (niacin or nicotinic acid) contains parts of two enzymes that regulate energy metabolism. It is essential for a healthy skin, tongue, and digestive system. Severe deficiency results in **pellagra**, mental disturbances, various skin eruptions, and GI disturbances. Pellagra may also occur during prolonged isoniazid therapy, and in cancer patients. Major sources of vitamin B3 include: lean meats, chicken, eggs, fish, cooked dried beans and peas, liver, nonfat or low-fat milk and cheese, soybeans, and nuts.

Vitamin B6. Vitamin B6 (pyridoxine) is a coenzyme essential for the synthesis and breakdown of amino acids, the conversion of tryptophan to niacin, the breakdown of glycogen to glucose, and

the production of antibodies. Therefore, vitamin B6 is important in the metabolism of blood, CNS, and skin.

Deficiency of pyridoxine is rare, because most foods contain vitamin B6. However, deficiency may result from malabsorption, alcoholism, oral contraceptive use. Vitamin B6 deficiency may cause anemia, anorexia, neuritis, nausea, dermatitis, and depressed immunity.

Vitamin B12. Vitamin B12 (hydroxocobalamin) is often found as **cyanocobalamin** in pharmaceutical preparations. It is involved in the metabolism of protein, fats, and carbohydrates. It aids in hemoglobin synthesis, is essential for normal functioning of all cells, and is important in energy metabolism. Vitamin B12 is available in meat and animal protein foods. Its absorption is complex; it occurs in the terminal portion of the small intestine (ileum) and requires **intrinsic factor** (a secretion of the stomach walls). Deficiency causes pernicious anemia and neurological disorders.

Vitamin C

Vitamin C (ascorbic acid) is essential for the formation of collagen tissue and for normal intercellular matrices in teeth, bone, cartilage, connective tissues, and skin. Ascorbic acid may protect the body against infections and help heal wounds. Therefore, ascorbic acid has multiple functions as either a coenzyme or cofactor. Its role in enhancing absorption of iron is well-recognized. Deficiency causes scurvy, lowered resistance to infections, joint tenderness, dental caries, bleeding gums, delayed wound healing, bruising, hemorrhage, and anemia.

14.2. Minerals

The major minerals are defined as those requiring an intake of more than 100 mg/day. The six major minerals are **calcium, phosphorus, chloride, sodium, potassium, and magnesium**.

Calcium (Ca) is the fifth-most abundant element in the human body and is present mainly in the bones. The body requires calcium ions for the transmission of nerve impulses, muscle contraction, blood coagulation, and cardiac functions. It is a component of extracellular fluid and of soft tissue cells.

Benign hypercalcemia due to excessive absorption of calcium may result in calcification of soft tissues and renal damage. Lack of calcium in the diet results in osteoporosis, in which bone is less dense, and therefore, brittle and weak.

Available calcium preparations are: -calcium gluconate, calcium citrate...

Zinc (Zn) is essential for several body enzymes, growth, glucose tolerance, wound healing, and taste acuity. Nearly all functional units of the immune system are adversely affected by zinc deficiency. It is also used in numerous pharmaceuticals, such as zinc acetate, zinc oxide, zinc permanganate, and zinc stearate. The best sources are protein foods. Zinc deficiency is characterized by abnormal fatigue, decreased alertness, a decrease in taste and odor sensitivity, poor appetite, retarded growth, delayed sexual maturity, prolonged healing of wounds, and susceptibility to infection and injury. Excess zinc supplementation can be dangerous as it can cause an increase in copper excretion, leading to copper deficiency. Other problems with excessive zinc intake are atherosclerosis due to a rise in cholesterol and triglyceride levels, and gastric irritation.

14.3. Electrolytes

Common electrolytes that are measured by clinicians using blood testing include sodium, potassium, chloride, and bicarbonate. Electrolytes are essential for homeostasis and play an important role in body chemistry. They circulate in the blood at specific levels where they are available when needed by the cells. An imbalance of electrolytes, such as when levels are too high or too low, can cause serious disease that requires treatment to restore balance in the body. Electrolytes are essential to many body functions such as nerve conduction, muscle contraction, and bone growth.

Intravenous fluids

IV solutions are used to replace fluids and electrolytes that have been lost or provide volume replacement that has been lost through hemorrhage, severe burns, diarrhea, vomiting, or inadequate fluid intake, to administer medication, to provide electrolyte balance, for amino acid utilization, and to monitor cardiac functions.

Common solutions used for intravenous administration include:

Dextrose 5% in sterile water (D5W): used for fluid loss, Dehydration, Hypernatremia

0.9% sodium chloride (normal saline, NS): Hyponatremia, Blood transfusion, Shock

Lactated ringers' solution: - It contains sodium, potassium, calcium and lactate. It is used for Burns, Dehydration, Acute hemorrhage.

Normal saline solution: - is an isotonic solution (0.9%) of sodium chloride.

Dextrose 5% and 0.9% sodium chloride (D5 NS): for temporary treatment for shock

Ammonium chloride: - given orally results in urinary acidification and is used in specialized diagnostic tests of renal tubular acidosis. It is a gastric irritant and is given as enteric-coated tablets.

Sodium bicarbonate causes urinary alkalization; intravenously it is used to alkalinize the urine in salicylate overdose. Alkalization of the urine is used to give symptomatic relief for the dysuria of cystitis and to prevent the formation of uric acid stones, especially in patients who are about to undergo cancer chemotherapy.

Activity

1. Visit your nearby pharmacy and list the nutritional and electrolyte solution available with their possible medical use
2. List the component and function each component found in oral rehydration solution (ORS)

15. Hair, beauty and cosmetic products

Dear trainees, at the end of this chapter, you will be able to apply product knowledge to provide accurate information to customers and other sales staff on cosmetic products.

15.1. Introduction

The word **cosmetic** is derived from the Greek word *kosmtikos* meaning having the power or skill to decorate. **Cosmetology** is the science of *beautifying* the skin and its appendages, which play an important role in socio-sexual communication. The scientific knowledge of cosmetology *enables to give rational treatments and aesthetically acceptable* results and prevent patient's indulgence in unscientific methods.

Cosmetics: are substances used to enhance or protect the appearance or odor of the human body. They are also defined as preparation that intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance. Their use is widespread, especially among women.

In another word cosmetics is:

- Product that helps improves external appearance and has the ability to hide, or at least distract from, unwanted stigmata or skin defects.
- A product that changes the color of hair is a cosmetic, as is a product intended to increase the skin's tendency to tan by exposure to sun.
- Laws and rules covering the distinction between cosmetics and drugs differ from country to country.
- Soap is specifically excluded from cosmetics in the FDCA (Food, Drug, and Cosmetics Act) and no cosmetic or drug regulations are applicable to soap.
- The devices used in applying the cosmetics as brush, comb razor blades they are not included in cosmetics

Cosmetics include

- Skin-care creams,
- Lotions, powders,
- Perfumes,
- Lipsticks,
- Fingernail and toenail polishes,
- Eye and facial makeup,
- hair colors,
- Hair sprays and gels,
- Deodorants,
- Baby products, bath oils,
- Bubble baths,
- Bath salts,
- Butters and many other types of products.

Therapeutic cosmetology

- Involves passage of active ingredients across the skin thereby altering the physiology of the area.

History of cosmetics

Archeological evidence of cosmetics dates at least from ancient Egypt and Greece. For instance, ancient Egypt used castor oil as a protective balm, skin creams made of beeswax, olive oil, and rosewater described by the Romans.

In the 1800s, make-up was used primarily by prostitutes, and Queen Victoria publicly declared makeup improper, and acceptable only for use by actors. In the 20th century there has been greatly progressed in the diversification of products and functions and in the safety and protection of the consumer.

The common cosmetic problems include:

- Acne (pimples),
- Diffuse hair loss,
- Excessive growth of hair,
- Scars;
- Premature ageing of skin;
- Excessive dryness of skin;
- Premature graying of hair;
- Pregnancy induced pigmentation on face etc.

Role of the Pharmacy professional

The pharmacy technician provides product information about:

- ingredients of the products
- the available brand options
- application procedures/techniques of specific products
- benefits and effects of various products
- customer personal requirements
- price of the products

Therefore, the expected function of pharmacy technicians is:

- Provide information on cosmetics
- Delivering product knowledge developed and maintained by accessing relevant sources of information.
- Storing product accurately according to product information and informing the consumers too.
- Transmitting product information to other staff members as required.
- Helping customer choose the best product suit to him/her
- Comparing between products and services researched and accurately applied according to product information.

Formulation and common ingredients of cosmetics

Cosmetics products are dissolved into or mixed with different kinds of chemical additives. The excipients may be used to bulk up cosmetic formulations with very potent target substances, to allow for convenient and accurate dosage. They are only used when absolutely necessary and in the smallest amounts possible.

The duration of cosmetic products is affected by denature of active ingredients, fall out of solution or stick to the sides of the container. So that the product may not stay for long. For these reasons, the product will be prepared with certain excipients that are important to keep the stability of the

cosmetic products. This ensures that the target ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time.

All ingredients in cosmetics, as well as their chemical decomposition products are to be identified and guaranteed to be safe.

The cosmetic product formula consists of :

- **Fillers/Diluents/vehicle:** fill out the amount of the product, making it practical to produce and convenient for the consumer to use.
- **Colour additives:** added to improve appearance of a formulation.
- **Lubricants:** added to prevent ingredients from clumping together and from sticking the processing machines.
- **An antioxidant:** preventing the oxidation of other additives
- **Fragrances:** Give the product a fresh, pleasing odor and cover up the smell of other ingredients.
- **Preservatives:** added to keep any product that includes water and oil from decay.
- **Humectants:** a substance that absorbs water from the air and hold the moisture in the skin or helps retain the moisture. **Humectants** must have appropriate water absorption ability, maintain moisture in the skin, have lowest possible volatility, be safe, be colorless, odorless and tasteless, and have densities matching the system they are used in. E.g. Glycerine, Propylene glycol, Sorbitol, Sodium lactate.
- **Emollients:** added to sooth and lubricate rough skin by fill in the spaces between the cells in the skin.

Classification of cosmetics

They can be classified based on widely used body parts as:

- | | |
|-----------------------------|------------------|
| ➤ Hair cosmetics | ➤ Nail cosmetics |
| ➤ Face cosmetics | ➤ Skin cosmetics |
| ➤ Eye make ups | ➤ Oral cosmetics |
| ➤ Lip decorators and carers | |

15.2. Hair cosmetics

- **Shampoos:** are based on soap or synthetic detergents which are used to cleanse, and leave the hair lustrous.
- **Hair conditioners:** is intended to reduce the magnitude of the forces associated with combing or brushing of the hair, especially when wet
- **Hair-coloring dyes (tint):** intended to give a younger appearance by making gray hairs less prominent, and also, they make hair more stylish by actively varying the color of the hair
- **Hair Tonics:** Are preparation which are applied to the hair for curing baldness, relieving oily or dry skin and to prevent or cure dandruff. It contains a combination of at least 2 to 3 ingredients i.e sebaceous gland stimulant, rubefacient and an antiseptic.
- **Hair growth promoter:** Are preparations made by adding various pharmaceutical agents to an alcohol-water solution which are applied to the scalp to normalize its functions
 - **Minoxidil** promotes a growth of fine hair any place on the skin where there are hair follicles.
- **Hair removers (depilatory):** Used to remove unwanted hair from the body. They are available as solid, semisolids (as cream form)

15.3. Face cosmetics

- **Face powder:** is a cosmetic powder applied to the face to set foundation.
 - **Characteristics of face powder:**
 - **It should be** very fine and should not have any gritty particles; the ingredients should be evenly distributed; non-toxic and non-irritant to the skin; chemically and physically stable; spread easily and adhere to the skin; good absorbing property; good to remove shine from the face, and so forth.
 - A **concealer** or **colour corrector;** is a type of makeup used to cover pimples, dark circles and other small blemishes visible on the skin. It is mainly used by women but also by some men

- **Rouge (Blush):** to redden the cheeks to provide a more youthful appearance, and to emphasize the cheekbones in the forms of compact, liquid, cream and stick. It is a cosmetic typically used by women.
- **Foundation:** skin colored cosmetics which give uniform color the face and conceal flaws (defect) to produce an impression of health and youth which are usually prepared as a liquid, cream, or powder.
- **Cold cream:** cosmetic preparation which applied to smooth face and remove makeup

15.4. Eye cosmetics (make up)

- **Eye liner:** is a cosmetic used to define the eyes to create a variety of beautiful appearance.
- **Eye shadow:** Is applied to eyelids and corners of the eyes to create shadow and produce a sense of relief in order to emphasize the beauty of the eyes.
 - The quality requirements for eye shadows include:
 - They should be easy to apply smoothly and have good skin adhesion
 - They should have no oily luster when applied
 - There should be no change in color
 - They should not be spoiled by sweat or sebum and maintain a good appearance
 - They should be highly safe as they used around the eyes
- **Mascara:** is a cosmetic used to darken, thicken and define eyelashes to emphasize, thicken, lengthen, and define lashes. It is available with tube and wand applicators.
 - Quality requirement for mascara are as follows.
 - They should: be non-irritating, not harden the eyelashes; make the eyelashes look thick and long, have an appropriate shine, have an appropriate drying time not go on the lower eyelids and their appearance, must not be spoiled by sweat, tears or rain; be easy to remove; be easy; and not be contaminated by microorganism.
- **Eye wrinkle care products:** are products that produce humectant effects used to prevent the skin around the eyes from drying.

- **Eyebrow cosmetics:** Are used after adjusting the form of the eyebrows with razors or scissors or by plucking out hairs to draw in the desired form, to make darker in color or brighter
- **Eye makeup remover:** To remove the different types of makeup

15.5. Nail cosmetics

- **Nail polish**
 - **Nail varnish or nail lacquers or nail enamels:** is a polish that is applied to the nails of both the fingers and toes, usually cosmetically for an aesthetic advantage

The perfect nail polishes

- Has to be easy to apply, and it should dry quickly
- Should leave a shiny, smooth, even, hard, and flexible film that is able to last five days
- Should be removed without leaving any trace and should not have any side effects
- Should be stable in the bottle
- Should offer a wide range of colors, enabling one to get the expected aesthetic effect

Unwanted Effects of Nail Polishes

- The nail polishes can cause an orange staining of the nail plate
- Nail lacquers can cause keratin granulation
- Nail varnishes can also cause allergic contact dermatitis, more rarely, contact urticarial

- **Nail Polish Remover**
 - Dissolve nitrocellulose and remove lipids from the nail plate.
 - They mainly contain a mixture of organic solvents, with small amounts of oils added to counteract the drying effect of the solvents.
 - Should not be used more than once a week and should not be left too long in contact with the nails and the skin

15.6. Skin cosmetics

These are cosmetics are applied to the dead cells of the corneal layer.

- Soap
- Skin cleansing liquids
- Skin moisturizers
- Skin whitening products
- Shaving preparations
- Antiperspirants and deodorants

The basic function of skin cosmetics

- Anti-drying, cleansing, ultraviolet damage prevention, anti-oxidation and invigoration
- Clean up skin problems
- Whitening effect to combat skin aging associated troubles
- Prevent wrinkles, sagging skin and acne
- To mask body odor

Moisturizers (emollients)

- Hold moisture in the skin.
- Work best when applied while the skin is still wet from a bath or shower.
- Don't actually add moisture to skin.
- Form a physical barrier that hinders evaporation of water from the skin.

Anti-aging cream

Moisturizer based skin care products marketed with the promise of making the consumer look younger by reducing visible wrinkles, expression lines, blemishes, pigmentation changes, discolorations of the skin.

- **Retinol:** to reduce fine lines and pores.
- **Epidermal Growth Factor:** to stimulate cell renewal and collagen production in the skin and strengthen elasticity and structure.
- **Alpha hydroxyl acids:** help dissolve the intracellular "glue" that holds the dead cells together on the skin and enhances the exfoliation of the dead cells.
- **Antioxidant**

Depilatories

- have the property of removing hair from the skin

Bronzers

- are cosmetic product that darken skin color

Antiperspirants and deodorants

- Cosmetics for preventing body odor contain antiperspirant perfumes and antibacterial agents

Antiperspirants

- are topically applied products designed to reduce underarm wetness by limiting eccrine sweat production?
- Zirconium and aluminum chlorides, aluminium hydrochloride, potassium aluminum sulfate, zinc oxide and zinc parphenolsulfonate

Deodorants: Are topically applied products designed to reduce underarm odor.

- **Application forms for deodorant actives**

- Typical application forms are sticks, roll-ons, creams, pump sprays, aerosols, and gels

Sunscreen formulation: block sun induced skin problem which are available in creams and lotions.

15.7. Lip decorators and carer

- **Lip gloss:** is a cosmetic product used to give the lips shine and sometimes subtle color prepared as a liquid or a soft solid.
- **Lip balm:** is a lip cosmetic product which generally has medicinal purposes
- **Lipstick (Lippy):** is a cosmetic product containing pigments, oils, waxes, and emollients that applies color and texture to the lips.

Quality of good lipstick, It should

- Be non-toxic and non-irritating
- Be free from gritty particles
- Be easily applicable and easily removable if need arises
- Be good odour
- Give shine and smooth appearance
- Be not dry on storage
- maintain its lip colour long after application
- not break during use and it should maintain its firmness till whole of it is used up

Oral cosmetics

- Divided into oral cleansing products and mouth fresheners oral cleansing products
- Preparation for external use which clean the teeth and surrounding them, cleanse and refresh the inside of the mouth, prevent dental caries and periodontal disease
- Divided in to **dentifrices** and **mouthwash**

Dentifrices

- Preparation meant to be applied to the teeth with a tooth brush for cleansing the accessible surfaces of the teeth to enhance appearance of the teeth, reduce tooth decay and bad odor of the mouth and make the gum healthy
- Dentifrices are found in the form of tooth powder, toothpaste and liquid-form dentifrices
- Ingredients include: polishing agents (abrasive), surface active agents (detergent), humectants, binders, sweetening agents, Flavoring agents, preservatives

Qualities of dentifrices

- It must remove foreign particles, food substances, plaque and clean the teeth
- Must be non-toxic
- Must be properly flavored and sweetened
- Must leave the mouth with a refreshing after-taste

Mouth washes (Mouth rinse): Used to clean the inside of the mouth, prevent halitosis and refresh the mouth.

- Similar in form to a liquid-form dentifrice but used without toothbrush
- Ingredients: ethanol, and other solvents, humectants, solubilizers, flavoring agents, preservatives and pH regulators

Mouth Freshener: Is preparation for internal use designed to prevent nausea and other feelings of discomfort.

- They are found in the form of pills, lozenges and liquids
- Ingredients used to flavor mouth fresheners have a strong freshening effect and include
 - cinnamon, mint oil, fennel oil, D-camphor, L-menthol
 - Depending on the form of mouth refreshner, other diluting agents, flavoring agents and preservatives are also used

Practice exercise: I. Match column “A” with column “B”

“A”

1. Face cosmetics
2. Eye cosmetics
3. Skin cosmetics
4. Oral cosmetics
5. Lip cosmetics

“B”

- A. Deodorants
- B. Lipstick
- C. Mascara
- D. Foundation
- E. Dentifrices

II. Write true for correct statements and false for incorrect statements

1. Cosmetics has no healing effects.
2. Soap is not considered as cosmetics.
3. Mouth fresheners is used to prevent nausea and other feelings of discomfort.
4. Moisturizers work best when applied while the skin is still wet from a bath or shower.
5. Mascara is a cosmetic used to darken, thicken and define eyelashes.

16. Pharmaceutical calculations

Dear trainees, at the end of this chapter, you will be able to:

-  Demonstrate how to convert weights and measures
-  Solve problems involving specific gravity, percent strength, weight in volume, weight in weight, and volume in volume
-  Demonstrate how to perform dilution and concentration calculations
-  Demonstrate use of mallequivalents

16.1. Introduction

Pharmaceutical calculation is the area of study that applies the basic principles of mathematics to the preparation and safe and effective use of pharmaceuticals. Correct pharmacy calculations are important to the practice of pharmacy. Pharmaceutical calculation encompasses calculation of amounts of components being added to a compounded total parenteral nutrition to the drops per minute rate on the label of an intravenous bag.

Pharmacy technician requires a variety of skills and abilities and perhaps most important is the ability to carry out important mathematic calculations. The goal of this module is to provide a basic review of the many types of pharmacy calculations that pharmacy technicians are required to be equipped with.

16.2. Measurement of weight and volume

Pharmaceutical measurement of weight and volume is an important part of pharmacy practice. The knowledge and application of pharmaceutical and clinical applications are essential for the practice of pharmacy.

The measurement systems include:

- i. Metric systems
- ii. Apothecary systems

iii. Household Systems

Many pharmaceutical calculations have been simplified by the shift from apothecary to metric system of measurements. In the household system of measurement, the patients use household measuring devices such as teaspoon, tablespoon, tea cup, wine glass. etc. though this system is inaccurate, due to increased home care delivery system are widely used. Therefore, only metric system will be discussed here.

1 Teaspoonful	= 5 ml
1 Tablespoonful	= 15 ml
1 Tea cupful	= 120 ml
1 Wine glassful	= 60 ml
1 Tumblerful	= 240 ml (1 full glass)

Volume measurement

The ***liter*** is the metric unit of volume. The table of metric volume follows:

1 liter(L)	= 0.001 kiloliter
	= 0.010 hectoliter
	= 0.100 decaliter
	= 10 deciliters
	= 100 centiliters
	= 1000 milliliters
	= 1,000,000 microliters

Common instruments for the pharmaceutical measurement of volume range from micropipets, and burettes used in analytic procedures to large, industrial-size calibrated vessels.

Examples of common containers for measuring volume are:

- ▶ Graduated Measuring Cylinders- 5ml,10ml,50ml
- ▶ Conical measures-100ml,200ml,250ml,500ml
- ▶ Beakers-100ml,200ml,300ml

An important factor in the accuracy of an instrument used for measuring volume is the surface area of the liquid in it. Accuracy increase as the surface area increases. However, a decrease in surface area decreases the convenience of transferring a liquid to and from the equipment. Therefore, accuracy and convenience should be compromised.

Measure of Weight

The unit of weight in the metric system is the **gram(g)**. The table of metric weights follows:

1 kilogram(Kg)	= 1000,000 grams
1 hectogram(hg)	= 100,000 grams
1 gram(g)	= 1,000 grams
1 milligram(mg)	= 0.001 grams
1 microgram (µg or mcg)	= 0.000,001 grams

The selection of balance and scale for weight measurements depends on the task at hand, from highly sensitive electronic analytic balances and prescription balances in extemporaneous compounding procedures to large-capacity scales in the industrial manufacturing and production of pharmaceutical products.

Weight is a measure of the gravitational force acting on a body, it is directly proportional to the body's mass. Weight is measured by means of a **balance**. In dispensing (hospital and community pharmacies), the type of balance used is called **Prescription balance**.

There are two main types of prescription balances:

1) Class A Prescription Balance

- Has a sensitivity requirement of 6mg with no load and with a load of 10g on each pan
- The maximum amount that can be weighed on this balance is 120g. E.g. Torison prescription balance

2) Class B Prescription Balance

- Has a sensitivity requirement of 30mg.

Their major purpose being the same (i.e. weighing), balances are differentiated from each other by the following parameters:

1. Sensitivity
2. Sensitivity Requirements
3. Capacity

Sensitivity

- ▶ Is the smallest weight that makes a perceptible change in the pointer of a balance which indicates the equilibrium position.

Sensitivity Requirements(SR)

- ▶ the minimum weight required to move the pointer by one division on the scale.
- ▶ SR for class A prescription Balance is 6mg while that of class B prescription balance is 30mg.
- ▶ N.B. The smaller the weight required to move the indicator one division, the more sensitive is the balance.

Capacity

- Is the maximum weight, which a balance can weigh.
- The capacity of most class A and class B prescription balance is 120g

$$\%Error = SR \times 100/\text{quantity to be weighed } (Q)$$

Percent error (%E) can also be figured by the formula given below:

$$\%E = \frac{|\text{Actual weight or volume} - \text{Intended weight or volume}|}{(\text{Intended weight or volume})} \times 100$$

Example

1. If a chlorpheniramine maleate tablet weighs 0.26gm, one-fourth of the same tablet weighs how many milligrams? Since the answer is required in milligrams, convert the weight of the tablet into milligrams first.

$$0.26\text{g}=0.26 \times 1000=260\text{mg}$$

$$1/4 \times 260\text{mg}=65\text{mg}$$

Answer: 65mg

2. Add 1.25g, 35mg and 80µg, and express the results in milligrams. Convert all the units into the same denomination and then perform the computation.

$$1.25\text{g}=1250\text{mg}, \text{ and } 80\mu\text{g} = 0.08\text{mg}$$

$$\text{Therefore, } 1250\text{mg}+0.08\text{mg}+35\text{mg}=1285.08\text{mg}$$

Answer, 1285.08mg

3. In calibrating a medicinal dropper, 2ml of a pediatric solution resulted in 48 drops. If it is desired to administer 0.08 mL of the medication to a baby approximately how many drops should be given?

$$48 \text{ drops } / 2\text{mL} = X \text{ drops } .0.08\text{mL}$$

$$X=1.922 \text{ or } 2 \text{ drops}$$

Answer =2 drops

4. What is a minimum amount that can be weighed on a class A prescription balance with a potential error of not more than 10%

$$\%Error = 100 \times 6\text{mg}/Q$$

$$Q=100 \times 6/10= 60\text{mg}$$

Answer = 60 mg

16.3. Density, specific gravity and specific volume

Density (d) is mass per unit volume of a substance. It is usually expressed as grams per cubic centimeter (g/cc). Density may be calculated by dividing mass by volume, that is:

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}}$$

Example

What is the density of hydrochloric acid weighing 20 mL and 40g?

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}} \quad \text{therefore, Density} = 40\text{g}/20\text{mL} = 2\text{g/mL}$$

Specific Gravity

Specific gravity (sp gr) is a ratio, *expressed decimally*, of the weight of a substance to the weight of an equal volume of a substance chosen as a standard, both substances at the same temperature or the temperature of each being known.

Specific gravity may be calculated by dividing the weight of a given substance by the weight of an equal volume of water, that is:

$$\text{Specific gravity} = \frac{\text{weight of substance}}{\text{Weight of equal volume of water}}$$

Because substances expand or contract at different rates when their temperatures change, accurate work necessitates allowing carefully for variations in the specific gravity of a substance.

In the United States Pharmacopeia, the standard temperature for specific gravities is 25°C, except for that of alcohol, which is 15.56°C by government regulation.

The density of a substance:

- ✚ is a concrete number (1.8 g/mL in the example),
- ✚ varies with the units of measure used

Specific gravity:

- ✚ A ratio between like quantities is an abstract number (1.8 in the example).
- ✚ Has no dimension and is therefore a constant value for each substance (when measured under controlled conditions).
- ✚ The specific gravity of water is always 1.
- ✚ Substances that have a specific gravity of less than 1 are lighter than water.

✚ Substances that have a specific gravity greater than 1 are heavier than water

Example 1

10ml of sulfuric acid weigh 18g, and 10ml of water, under similar conditions, weigh 10g, the specific gravity of the acid is:

$$\text{Specific gravity} = \frac{18\text{g}}{10\text{ml}} = 1.8$$

Example 2

If 52.5 mL of oil weighs 48.8 g, what is the specific gravity of the oil?

Answer

52.96 mL of water weighs 52.5gm. Therefore, specific gravity of the oil= 48.8/52.5=0.929

Calculating the specific gravity of liquids

A *pycnometer* is a special glass bottle used to determine specific gravity. To calculate the specific gravity of a liquid by means of a specific gravity bottle, the container is filled and weighed first with water and then with the liquid. By subtracting the weight of the empty container from the two weights, we have the weights of equal volumes, even though we may not know the volumes exactly.

Example:

A specific gravity bottle weighs 23.66 g. When filled with water, it weighs 72.95 g; when filled with another liquid, it weighs 73.56 g. What is the specific gravity of the liquid?

Answer, $73.56 \text{ g} - 23.66 \text{ g} = 49.90 \text{ g}$ of liquid

$72.95 \text{ g} - 23.66 \text{ g} = 49.29 \text{ g}$ of water

Specific gravity of liquid

$= 49.90 \text{ (g)} / 49.29 \text{ (g)}$

$= 1.012$, answer.

Calculating the specific gravity of solids using displacement methods

To calculate the specific gravity of a solid *heavier than* and *insoluble in water*, simply divide the weight of the solid in air by the weight of water that it displaces when immersed in it. The weight of water displaced (apparent loss of weight in water) is equal to the *weight of an equal volume of water*.

Example:

A piece of glass weighs 38.525 g in air and 23.525 g when immersed in water. What is its specific gravity?

$38.525\text{ g} - 23.525\text{ g} = 15\text{ g}$ of displaced water (weight of an equal volume of water)

Sp.gr. Of glass = $\frac{38.525\text{ g}}{15\text{ g}} = 2.568$, answer

15 g

Specific Volume

Specific volume, in pharmaceutical practice, is usually defined as an abstract number representing the ratio, expressed decimally, of the volume of an equal weight of another substance taken as a standard, both having the same temperature. Water is the standard for liquids and solids. It may be calculated by dividing the volume of a given mass by the volume of an equal weight of water.

Example

If 25g of glycerin measure 20ml and 25 g of water measure 25 ml under the same conditions, the specific volume of the glycerin is:

$$\frac{\text{Volume of 25 g of glycerin}}{\text{Volume of 25 g of water}} = \frac{20\text{ ml}}{25\text{ ml}} = 0.8$$

$$\frac{\text{Volume of 25 g of glycerin}}{\text{Volume of 25 g of water}} = \frac{20\text{ ml}}{25\text{ ml}} = 0.8$$

Because specific gravity and specific volume are reciprocals, a substance that is heavier than water will have a higher specific gravity and a lower specific volume, whereas a substance that is lighter than water will have a lower specific gravity and a higher specific volume.

It follows, therefore, that we may determine the specific volume of a substance by dividing 1 by its specific gravity, and we may determine the specific gravity of a substance by dividing 1 by its specific volume.

Examples:

What is the specific volume of phosphoric acid having a specific gravity of 1.71?

$$\frac{1}{1.71} = 0.585, \text{ answer}$$

$$\frac{1}{1.71}$$

If a liquid has specific volume of 1.396, what is its specific gravity?

$$\frac{1}{1.396} = 0.716, \text{ answer}$$

1.396

Use of Specific Gravity in Calculations of Weight and Volume

The weights of equal volumes and the volumes of equal weights of liquids are proportional to their specific gravities. To calculate, therefore, the weight of a given volume or the volume of a given weight of a liquid, its specific gravity must be known. When specific gravity is used as a factor in a calculation, the result should contain no more significant figures than the number in the factor. Because of the simple relationship between the units in the metric system, such problems are solved simply and easily when only metric quantities are involved, but they become more complex when units of the common systems are used.

Examples:

1. What is the weight, in grams, of 3620 mL of alcohol with a specific gravity of 0.820?

Grams = Milliliters x Specific gravity

3620 mL of water weigh 3620 g

$3620 \text{ g} \times 0.820 = 2968 \text{ g}$, answer

2. What is the volume, in milliliters, of 492 g of nitric acid with a specific gravity of 1.40?

492 g of water measure 492 mL

$492 \text{ mL} / 1.4$

$= 351 \text{ mL}$, answer

Activity

Solve the following problem

1. If a liter of a cough syrup weighs 1285 g, what is its specific gravity?
2. What is the weight of 60 ml of oil whose density is 0.9624 g/ml?
3. A prescription calls for 0.3 g of phosphoric acid with a specific gravity of 1.71. How many milliliters should be used in compounding the prescription?
4. If a prescription order requires 25 g of concentrated HCl (Density 1.18 g/ml), what volume should the druggist measure?
5. A piece of copper metal weighs 53.6 g, and has a volume of 6ml. Calculate its density.
6. If chloroform has a specific gravity of 1.476, what is its specific volume?

16.4. Ratio, proportion and percentage calculation

Ratio and proportion

Ratio

A ratio indicates a relation or comparison of two like quantities. It can be expressed as quotient, a fraction, a percentage, or a decimal. Ratio is used to compare two different things.

Examples:

Quotient: $1 \div 2 = 1:2$ or 1 is to 2

Fraction: $\frac{1}{4} = 1:4$ or 1 is to 4

Percentage: 20% or 20:100 or 20 is to 100

Decimal: $0.15 = 15/100$ or 15 is to 100

Two equal fractions can be written as a proportion. Thus, a proportion is a statement of equality between two fractions or ratios. The following forms may be used to express the proportions:

$$a:b=c:d$$

$$a/b=c/d$$

Examples of equal fractions written as proportions:

$$12/15=4/5$$

$$3/6=21/42$$

$$8/16=22/44$$

$$\text{If } \frac{a}{b} = \frac{c}{d}$$

$$\text{then, } \frac{b}{a} = \frac{d}{c}$$

other forms of expression:

$$a = \frac{b \times c}{d}$$

or:

$$b = \frac{a \times d}{c}$$

Examples

1. If 3 tablets contain 975 milligrams of aspirin, how many milligrams should be contained in 12 tablets?

$$\frac{3 \text{ (tablets)}}{12 \text{ (tablets)}} = \frac{975 \text{ (milligrams)}}{X \text{ (milligrams)}}$$

$$12 \text{ (tablets)} \times X \text{ (milligrams)}$$

$$X = \frac{12 \times 975}{3} = 3900 \text{ milligrams}$$

Percentage

The term percent and its corresponding sign (%) mean “by the hundred,” and percentage means “rate per hundred”; so, 50 percent of 50 are equivalent expressions. A percent may also be expressed as a ratio, represented as a common or a decimal fraction.

For Example: -50% means 50 parts in 100 of the same kind, and may be expressed as 50/100 or 0.50. For the purpose of computation, percents are usually changed to equivalent decimal fractions. This change is made by dropping the percent sign (%) and dividing the expressed numerator by 100.

Percentage is an essential part of pharmaceutical calculations. The pharmacy professionals encounter it frequently and uses it as a convenient means of expressing the concentration of an active or inactive material in a pharmaceutical preparation

The percentage concentrations of active and inactive constituents in various types of pharmaceutical preparations are defined as follows by the USP.:

- Percentage weight-in-volume (w/v)
- Percentage volume-in-volume (v/v)
- Percentage weight-in-weight (w/w)

Percent weight-in-volume (% w/v)

Expresses the number of grams of a constituent in 100ml of solution or liquid preparation, and is used regardless of whether water or another liquid is the solvent or vehicle.

- For solutions or suspensions of solids in liquids
- For solutions of gases in liquids

Example

1. How many grams of dextrose are required to prepare 4000ml of a 5% solution?

4000ml represent 4000g of a solution

$$5\% = 0.05$$

$$4000\text{g} \times 0.05 = 200\text{g}$$

2. How many grams of potassium permanganate should be used in compounding the following prescription?

Rx Potassium permanganate 0.02%

purified water ad 250ml

sig. As directed.

250ml represent 250g of solution

$$0.02\% = 0.0002$$

$$250\text{ g} \times 0.0002 = 0.05\text{g, answer}$$

Weight in weights

Express the number of grams of a constituent in 100g of solution or preparation.

Examples:

1. How many grams of phenol should be used to prepare 240 g of a 5% (w/w) solution in water?

weight of solution (g) x % (expressed as a decimal) = g of solute

$$240\text{g} \times 0.05 = 12\text{g, answer}$$

2. *How many grams of a drug substance are required to make 120 mL of a 20% (w/w) solution having a specific gravity of 1.15?*

120ml of water weigh 120g

$$120\text{ g} \times 1.15 = 138\text{ g, weight of 120ml of solution}$$

$$138\text{ g} \times 0.2 = 27.6\text{ g plus enough water to make 120ml, answer}$$

Or, solving by dimensional analysis

$$120\text{ml} \times \frac{1.15\text{g}}{1\text{ml}} \times \frac{20\%}{100\%}$$

$$1\text{ml} \quad 100\%$$

$$X = 27.6\text{ g , answer}$$

Volume in volume

Liquids are usually measured by volume, and the percentage strength indicates the number of parts by volume of an ingredient contained in the total volume of the solution or liquid preparation considered as 100 parts by volume.

Example:

1. How many milliliters of a liquid phenol should be used in compounding the following prescription?

R_x _Liquefied phenol 2.5%

Calamine lotion ad 240ml

sig. For external use.

Volume(ml) x % (expressed as a decimal) = milliliters of active ingredient

$$240\text{ml} \times 0.025 = 6\text{ml, answer}$$

2. What is the percentage strength(v/v) of a solution of 800g of a liquid with a specific gravity of 0.8 in enough water to make 4000ml?

800 g of water measure 800ml

$$800\text{ ml} \div 0.8 = 1000\text{ml of active ingredient}$$

$$\frac{4000(\text{ml})}{1000(\text{ml})} = \frac{100(\%)}{X(\%)}$$

$$1000(\text{ml}) \quad X(\%)$$

$$X = 25\%, \text{ answer}$$

Or, Solving by dimensional analysis:

$$\frac{800\text{ml}}{0.8} \times \frac{1}{4000\text{ml}} \times 100\% = 25\%$$

Calculating the volume of a solution or liquid preparation, given the volume of the active ingredient and its percentage strength (v/v), may require first determining the volume of the active ingredient from its weight and specific gravity.

Examples:

1. Peppermint spirit contains 10% (v/v) of peppermint oil. What volume of the spirit will contain 75ml of peppermint oil?

$$\frac{10(\%)}{100(\%)} = \frac{75(\text{ml})}{X(\text{ml})}$$

$$100(\%) \quad X(\text{ml})$$

$$X = 750\text{ml}, \text{ answer}$$

Parts per million

The strengths of very dilute solutions are commonly expressed in terms of parts per million (ppm). For example, we are all familiar with fluoridated drinking water in which fluoride has been added at levels of between 1 to 4 parts per million (1:1,000,000 to 4:1,000,000) for the purpose of reducing dental caries. We also are aware of and concerned with the presence of trace amounts of contaminants in our drinking water and food which can pose a risk to our health and safety. Many persons have food allergies, immune system disorders, and other conditions that render them more at risk than the general population. Other environmental contaminants are also expressed by parts per million.

Example

1. Express 5 ppm of iron in water in percentage strength and ratio strength.

$$5 \text{ ppm} = 5 \text{ parts in } 1,000,000 \text{ parts} = 1:200,000, \text{ ratio strength, and} \\ = 0.0005\%, \text{ percentage strength, answers.}$$

Millimoles and milliequivalents

Most electrolyte solutions are measured by milliequivalents (mEq), which are related to molecular weight. Molecular weights are based on the atomic weights of common elements. You may recall the periodic elements table posted on the wall in your chemistry class.

The atomic weight of an element is the weight of a single atom of that element compared with the weight of one atom of hydrogen. The molecular weight of a compound is the sum of the atomic weights of all the atoms in one molecule of the compound.

A **millimole (mM)** is the molecular weight expressed as milligrams. Thus 1 mM of sodium chloride equals 58.5 mg.

Mole (M) the measurement of an element equal to its atomic weight in grams. Thus 1 M of sodium (Na) is equal to 22.9898 g, which is typically rounded to 23 g. Compounds are also measured in moles. For example, the atomic weight of 1 M of salt or sodium chloride (NaCl) would equal the sum of the weight of its components. atomic weight of sodium (23 g) 1 atomic weight of chlorine (35.5 g) 5 58.5 g.

As stated before, 1 mM is the molecular weight expressed in milligrams. Because 1 g equals 1000 mg, 1 M equals 1000 mM.

The valence of an element is a number that represents its capacity to combine to form a molecule of a stable compound. An element can exist in various forms. Valence may vary depending on an elemental form.

One **milliequivalent (mEq)** is equal to 1 mM divided by its valence.

$$1 \text{ mEq} = \frac{\text{atomic weight (mg)}}{\text{valence}}$$

$$\text{mEq} = \frac{\text{mg} \times \text{Valence}}{\text{Atomic, formula, or molecular weight}}$$

$$\text{mg} = \frac{\text{mEq} \times \text{Atomic, formula, or molecular weight}}{\text{Valence}}$$

$$\text{mg/mL} = \frac{\text{mEq / mL} \times \text{Atomic, formula, or molecular weight}}{\text{Valence}}$$

A milliequivalent is a unit of measurement of the amount of chemical activity of an electrolyte. It is related to the total number of ionic charges in solution and it takes the valence of ions into consideration.

Example

1. Sodium has an atomic weight of 23 mg and a valence of 1. How many milliequivalents are in 92 mg of sodium?

Step 1. Determine the weight of 1 mEq of sodium by dividing the molecular weight (from the atomic weight) by the valence.

$$1 \text{ mEq} = \text{molecular weight} / \text{valence} \quad \text{i.e.} \quad 23 \text{ mg} / 1 = 23 \text{ mg}$$

Step 2. Determine the number of milliequivalents in 92 mg of sodium.

$$\text{mEq} = \text{weight of sodium} / \text{weight of 1 mEq} = 92 \text{ mg} / 23 \text{ mg} = 4 \text{ mEq}$$

Determining the Milliequivalents of Compounds

The first step in determining the number of milliequivalents of a compound is to identify the formula of the compound. The next step is to separate the formula into atoms. The atomic weight of each atom is then multiplied by the number of those atoms, the products are added together, and that sum is substituted into the formula for atomic weight.

Example

1. What is the milliequivalent weight of potassium chloride?

Molecular weight of KCL=74.5

KCL has a valence of 1

milliequivalent weight $74.5/1=74.5\text{mg}$

2. The molecular weight of magnesium sulfate ($\text{Mg}^{+2} \text{SO}_4^{-2}$) is 120 mg and its valence is 2. How many milligrams does 1 mEq of magnesium sulfate weigh?

$1 \text{ mEq} = \text{molecular weight} / \text{valence}$

$$1 \text{ mEq} = 120 \text{ mg} / 2 = 60 \text{ mg}$$

3. A solution contains 10 mg/100 mL Ca^{++} ions. Express this concentration in terms of mEq/L (Mol. Weight=40)

$$\text{mEq} = 40/2 = 20 \text{ and therefore, } 10\text{mg} = 5 \text{ mEq}$$

$$\text{mEq/L} = 5 \text{ mEq/L}$$

16.5. Dilution, concentration and reconstitution

We considered problems arising from the quantitative relationship between specific ingredients and the pharmaceutical preparation as a whole.

Problems of a slightly different character arise when pharmaceutical preparations are:

Diluted by:

- ▶ the addition of diluent, or
- ▶ admixtures with solutions, or
- ▶ mixtures of lower strength) and

Concentrated by:

- the addition of active ingredients, or
- Mixtures of greater strength, or
- Evaporation of the diluent

Such problems sometimes seem complicated and difficult. But the complications proves to be nothing more than a series of steps required in the calculation, and the difficulty usually vanishes as each step, in itself, proves to be a simpler matter.

These two rules, wherever they may be applied, greatly simplify the calculation:

1. *When ratio strengths are given, convert them to percentage strengths before setting up a proportion.*

✚ It is more troublesome to calculate with a ratio like 1/10: 1/500 than with the equivalent 10(%): 0.2(%)

2. *whenever proportional parts enter into a calculation, reduce them to lowest terms.*

✚ Instead of calculating with a ratio like 75(parts): 25(parts), simplify it to 3(parts): 1 part.

Relationship between Strength and Total Quantity

If a mixture of a given percentage or ratio strength is diluted to twice its original quantity, its active ingredient will be contained in twice as many parts of the whole, and its strength therefore will be reduced by one half.

Contrariwise, if a mixture, is concentrated by evaporation to one-half its original quantity, the active ingredient (assuming that none was lost by evaporation) will be contained in one –half as many parts of the whole, and the strength will be doubled.

So, if the 50ml of a solution containing 10 g of active ingredient with strength of 20% or 1:5 (w/v) are diluted to 100ml, the original volume is doubled, but the original strength is now reduced by one-half to 10% or 1:10(w/v).

If by evaporation of the solvent, the volume of the solution is reduced to 25ml or one-half the original quantity, the 10g of the active ingredient will indicate strength of 40% or 1:2.5(w/v).

If, then, *the amount of active ingredient remains constant, any change in the quantity of a solution or mixture of solids is inversely proportional to the percentage or ratio strength*; i.e., the percentage or ratio strength decreases as the quantity increases, and conversely.

This relationship is generally true for all mixtures except volume – in – volume and weight – in – volume solutions containing components that contract when mixed together. Example alcohol.

Problems in this section generally may be solved by:

1. Inverse proportion;
2. The equation:

$$(\text{quantity 1}) \times (\text{concentration 1}) = (\text{quantity 2}) \times (\text{concentration 2})$$

$$Q_1 \times C_1 = Q_2 \times C_2$$

Determining the quantity of active constituent(solute) needed and then calculating the quantity of the available solution (usually concentrated or stock solution) that will provide the needed amount of constituent.

Determination of percentage or Ratio strength:

Calculating the percentage or ratio strength of a solution made by diluting or concentrating (by evaporation) a solution of a given quantity and strength involves the following:

Examples:

1. If 500ml of a 15% (v/v) solution of methyl salicylate in alcohol are diluted to 1500 ml, what will be the percentage strength (v/v)?

$$\frac{1500 \text{ ml}}{500 \text{ ml}} = \frac{15 \%}{X} \quad X = 5 \%$$

500 ml X %

Or,

$$Q1(\text{quantity}) \times C1(\text{concentration}) = Q2(\text{quantity}) \times (\text{Concentration})$$

$$500 \times 15 \% = 1500 \text{ ml} \times X \%$$

2. If a syrup containing 65 % (w/v) of sucrose is evaporated to 85 % of its volume, what percent (w/v) of sucrose will it contain?

Any convenient amount of the syrup, e.g., may be used in the calculation. If we evaporate 100 ml of the syrup to 85% of its volume, what is volume, we will have 85 ml.

$$\frac{85 \text{ ml}}{100 \text{ ml}} = \frac{65 \%}{X \%}$$

$$100 \text{ ml} \quad X \%$$

$$X = 76.47\% \text{ or } 76 \%$$

Determining Amount of Solution of a Desired Strength:

Calculating the amount of solution of desired strength that can be made by diluting or concentrating (by evaporation) a specified quantity of a solution of a given involves the following:

Examples:

1. How many grams of 10 % (w/w) ammonia solution can be made from 1800 g of 28% (w/w) strong ammonium solution?

$$Q1 \times C2 = Q2 \times C1$$

$$1800 \text{ g} \times 28 \% = X \text{ g} \times 10 \%$$

$$X = 5040 \text{ g}$$

Stock Solutions

Stock solutions are solutions of known concentration that are prepared by the pharmacy professionals for convenience in dispensing. They are usually strong solutions from which weaker ones may be made conveniently. When correctly prepared, these solutions enable the pharmacy professionals to obtain small quantities of medicinal substances that are to be dispensed in solution. Stock solutions usually are prepared on a weight – in – volume basis, and their concentration is expressed as ratio strength or, less frequently, as percentage strength.

Calculating the amount of a solution of a given strength that must be used to prepare a solution of desired amount and strength involves the following:

Examples:

1. How many milliliters of a 1: 400 ml (w/v) stock solution should be used to make 4 liters of a 1:2000 (w/v) solution?

$$4 \text{ liters} = 4000 \text{ ml}$$

$$1:400 = 0.25\% \quad 1:2000 = 0.05\%$$

$$Q_1 \times C_1 = Q_2 \times C_2$$

$$4000 \text{ ml} \times 0.25\% = X \times 0.05\%$$

$$X = 800 \text{ ml}$$

When given the quantity and strength of a solution, we may determine how much diluent should be added to reduce its strength as desired by first calculating the quantity of weaker solution that can be made and then subtracting from this the original quantity.

Examples:

1. How many of water should be added to 300ml of a 1: 750 (w/v) solution of benzakonium chloride to make a 1:2500 (w/v) solution?

$$1: 750 = 0.133\% \quad 1: 2500 = 0.04\%$$

$$0.04\% = \frac{300 \text{ ml}}{X \text{ ml}}$$

$$0.133\% \quad X \text{ ml}$$

$X = 997.5 \text{ ml}$ or 1000ml of 0.04 % (w/v) solution to be prepared.

The difference between the volume of diluted (weaker) solution prepared and the volume of stronger solution used represents the volume of water (diluent) to be used.

$$1000 \text{ ml} - 300 \text{ ml} = 700 \text{ ml, answer.}$$

Triturations

Triturations are dilutions of potent medicinal substances. They were at one time official and were prepared by *diluting one part by weight of the drug with nine parts of finely powdered lactose*. they are, therefore, 10% or 1:10(w/w).

Note: The term “trituration” as used in this context should not be confused with the like term *trituration*, which is the pharmaceutical process of reducing substances to fine particles through grinding in a mortar and pestle.

Quantity of Trituration Required to obtain Given Amount of Medicinal Substance.

Examples:

How many grams of a 1:10 trituration are required to obtain 25 mg of drug?

10 g of trituration contain 1 g of drug

$$25 \text{ mg} = 0.025 \text{ g}$$

$$\underline{1 \text{ g}} = \underline{10 \text{ g}}$$

$$0.025 \text{ g} \quad X \text{ g}$$

$$X = 0.25 \text{ g, answer}$$

Alligation

Alligation is an arithmetical method of solving problems that involve the mixing of solutions or mixtures possessing different percentage strengths. *Alligation medial* is a method by which the “weighted average” percentage strength of a mixture of two or more substances of known quantity and concentration may be easily calculated.

By this method, the percentage strength of each component, expressed as a decimal fraction, is multiplied by its corresponding quantity; and the resultant decimal fraction is multiplied by 100 to give the percentage strength of the mixture. Of course, the quantities must be expressed in a common denomination, whether of weight or volume.

Examples:

1. What is the percentage strength (v/v) of alcohol in a mixture of 3000 ml of 40 % (v/v) alcohol, 1000 ml of 60 % (v/v) alcohol, and 1000 ml of 70 % (v/v) alcohol? Assume no contraction of volume after mixing.

$$0.4 \times 3000 \text{ ml} = 1200 \text{ ml}$$

$$0.6 \times 1000 \text{ ml} = 600 \text{ ml}$$

$$0.7 \times \underline{1000 \text{ ml}} = \underline{700 \text{ ml}}$$

$$\text{Totals} = 5000 \text{ ml} \quad 2500 \text{ ml}$$

$$2500 \text{ ml} \div 5000 \text{ ml} = 0.5 \times 100 = 50 \%, \text{ answer}$$

Reconstitution

Some drugs must be stored in powdered form because they rapidly lose their power once they are mixed into a solution. These drugs will then have to be reconstituted, or mixed with a liquid, called the diluent, before they can be administered.

Medications that are unstable in liquid form for extended periods of time are manufactured in either a powder or crystalline (lyophilized) form for reconstitution before use. To reconstitute a

medication, care must be taken to follow the instructions on medication label *exactly*. Before using the medication, care must be taken that the dry ingredients are completely dissolved or suspended into liquid form by adding a diluent.

When used as an injectable medication, single-dose vials/ampules or multi dose vials are available. Available multi dose containers are used when a number of doses may be used from the same container within the amount of time that is with the safe time limit after reconstitution. The diluents used for reconstitution for injectable medications must be sterile and may come in a single-dose vial, as for reconstitution of immunizations that are single doses, or in multi dose vials such as sterile water for injection used for multiple doses of antibiotics. To reconstitute injectable medications, sterile syringes are used in the appropriate size for the amount of diluent necessary for the manufacturer's label.

Examples

Bottle of Oxacillin contain 2 g powder

Directions on label: add 11.5cc

Sterile H₂O for injection

Each 1.5 cc = 250 mg

Dose ordered is 500mg IM

How many _____ cc's will we give?

$250 \text{ mg} / 1.5 \text{ cc} = 500 \text{ mg} / X \text{ cc}$

$250X = 500 \text{ mg} \times 1.5$

$250X = 750$

$X = 3 \text{ cc}$

Self-Check questions

1. If a liter of mannitol weighs 1285gm, what is the specific gravity and specific volume of the substance?
2. If 73.42 g of a liquid measures 81.5 mL, what is its specific volume?
3. The specific gravity of alcohol is 0.815. gravity. What is its specific volume?
4. If 500 mL of ferric chloride solution weighs 650 g, what is its specific gravity?
5. If 250 mL of alcohol weighs 203 g, what is its density?
6. A balance has a sensitivity requirement of 0.4mg. what is the smallest weight that can be weighted accurately with an error of not more than 3%?
7. Convert the following strength into %strength, and PPM
 1:25000 B. 1:500 C. 1: 100000
8. 5ml of a 20% solution was diluted to 50ml. what is the final strength of the solution?
9. How many grams of a drug is used in preparing a 50-ml stock solution such that 2-ml diluted to 100ml will yield a 0.25%w/v solution?
10. What is the % strength and ratio strength of a drug solution prepared by mixing 50 ml of 15%, 10 ml of 10% and enough solvent to make 100 ml?
11. How many mg of a 10% ZnO must be mixed with a 15% ZnO to get 100mg of 5%ZnO?
12. A 1 in 10 000 solution of potassium permanganate contains which of the following concentrations?
 - A. 50.0 mg potassium permanganate in 500 mL solution
 - B. 1.0 mg potassium permanganate in 100 mL solution
 - C. 5.0 mg potassium permanganate in 500 mL solution
 - D. 1.0 mg potassium permanganate in 1000 mL solution
 - E. 3.0 mg potassium permanganate in 300 mL solution

13. Which of the following amounts of copper sulphate is required to make 400 mL of an aqueous stock solution, such that, when the stock solution is diluted 50 times with water, a final solution of 0.1% w/v copper sulphate is produced?
- A. 0.2 g
 - B. 20.0 g
 - C. 0.4 g
 - D. 40.0 g
 - E. 50.0 g
14. Potassium permanganate solution 1 in 8000 is prepared from a stock of 10 times this strength. How much potassium permanganate will be needed to make sufficient stock solution if a patient uses 200 mL of the diluted solution each day for 20 days?
- A. 100 mg
 - B. 125 mg
 - C. 250 mg
 - D. 400 mg
 - A. 500 mg
15. What volume of phenytoin suspension 30 mg/5 mL is required to be added to a suitable diluent to obtain 150 mL phenytoin suspension 20 mg/5 mL?
- A. 75 mL
 - B. 100 mL
 - C. 120 mL
 - D. 125 mL
 - E. 130 mL
16. Given a 20% w/v solution of chlorhexidine gluconate, what volume is required to make 400 mL of a 2% w/v solution?
- A.** 40 mL
 - B.** 20 mL
 - C.** 80 mL
 - D.** 2 mL
 - E.** 4 mL

17. An injection solution contains 0.5% w/v of active ingredient. How much of the active ingredient is needed to prepare 500 L of solution?
- A. 0.25 kg
 - B. 0.50 kg
 - C. 1.00 kg
 - D. 2.50 kg
 - E. 5.00 kg
18. How many milliliters of 28% w/w strong ammonia solution having a specific gravity of 0.89 should be used in preparing 2000 mL of 10% w/w ammonia solution with a specific gravity of 0.96?

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Annex I: Examples of Specific Antidotes

Antidote	Poison(s)	Comments
Acetylcysteine (Acetabate, Mucomyst)	Acetaminophen	Best results if given within 8–10 hours of overdose. Follow liver function tests and acetaminophen blood levels. Acetabate is given intravenously; Mucomyst, orally.
Atropine	Anticholinesterases: organophosphates, carbamates	A test dose of 1–2 mg (for children, 0.05 mg/kg) is given IV and repeated until symptoms of atropinism appear (tachycardia, dilated pupils, ileus). Dose may be doubled every 10–15 minutes, with decrease of secretions as therapeutic end point.
Bicarbonate, sodium	Membrane-depressant cardiotoxic drugs (tricyclic antidepressants, quinidine, etc)	1–2 mEq/kg IV bolus usually reverses cardiotoxic effects (wide QRS, hypotension). Give cautiously in heart failure (avoid sodium overload).
Calcium	Fluoride; calcium channel blockers	Large doses may be needed in severe calcium channel blocker overdose. Start with 15 mg/kg IV.
Deferoxamine	Iron salts	If poisoning is severe, give 15 mg/kg/h IV. Urine may become pink. 100 mg of deferoxamine binds 8.5 mg of iron.
Digoxin antibodies	Digoxin and related cardiac glycosides	One vial binds 0.5 mg digoxin; indications include serious arrhythmias, hyperkalemia.
Esmolol	Theophylline, caffeine, metaproterenol	Short-acting β blocker reverses β_1 -induced tachycardia and (possibly) β_2 -induced vasodilation. Infuse 25–50 mcg/kg/min IV.
Ethanol	Methanol, ethylene glycol	Ethanol therapy can be started before laboratory diagnosis is confirmed. A loading dose is calculated so as to give a blood level of at least 100 mg/dL (42 g/70 kg in adults).
Flumazenil	Benzodiazepines	Adult dose is 0.2 mg IV, repeated as necessary to a maximum of 3 mg. <i>Do not give to patients with seizures, benzodiazepine dependence, or tricyclic overdose.</i>
Fomepizole	Methanol, ethylene glycol	More convenient and easier to use than ethanol. Loading dose 15 mg/kg; repeat every 12 hours.

Glucagon	β blockers	5–10 mg IV bolus may reverse hypotension and bradycardia that was resistant to β -agonist drugs. May cause vomiting.
Naloxone	Narcotic drugs, other opioid derivatives	A specific antagonist of opioids; 1–2 mg initially by IV, IM, or subcutaneous injection. Larger doses may be needed to reverse the effects of overdose with propoxyphene, codeine, or fentanyl derivatives. Duration of action (2–3 hours) may be significantly shorter than that of the opioid being antagonized.
Oxygen	Carbon monoxide	Give 100% by high-flow nonrebreathing mask; use of hyperbaric chamber is controversial.
Physostigmine	Suggested for antimuscarinic anticholinergic agents; not for tricyclic antidepressants	Adult dose is 0.5–1 mg IV slowly. The effects are transient (30–60 minutes), and the lowest effective dose may be repeated when symptoms return. May cause bradycardia, increased bronchial secretions, seizures. Have atropine ready to reverse excess effects. <i>Do not use for tricyclic antidepressant overdose.</i>
Pralidoxime (2-PAM)	Organophosphate cholinesterase inhibitors	Adult dose is 1 g IV, which should be repeated every 3–4 hours as needed or preferably as a constant infusion of 250–400 mg/h. Pediatric dose is approximately 250 mg. No proved benefit in carbamate poisoning.

Module Syllabus

Module title: Basic Concepts in Pharmaceutical Sciences I

Module code: PRA2M1017

Nominal duration: 480 Hours (10 weeks): theory (352 hrs.) + practical (128hrs)

Module Description:

This module aims to provide the learners with the basic knowledge of drugs, and identify nutritional and cosmetic products and recommend to clients.

Unit of Competencies

- Assist in Dispensary Operations
- Recommend Hair, Beauty and Cosmetic Products and Services
- Recommend Health and Nutritional Products and Services

Module Objective

By the end of this module, you will be able to

- Describe pharmacokinetic processes (ADME)
- Describe pharmacodynamics (drug targets, agonists, antagonists, efficacy, potency, Therapeutic Index)
- List factors affecting drug actions
- Identify type drug interactions
- For each body system listed under the outlines:
 - Describe overview of anatomy and physiology
 - Describe indications, common adverse effects, major contraindications and significant interaction of drugs that affect the system
 - List drugs class in each system
- Describe indications, common adverse effects, major contraindications and significant interaction of chemotherapeutic agents
- List drugs used in cancer
- List drugs used for common skin disorders
- Identify and handle common vaccines and immunological products available in Ethiopia
- Categorize drugs based on pharmacological classes
- Classify drugs based on therapeutic application
- Predict if there is interaction between two given drugs/drug and food
- Define dosage forms
- Describe major composition of medication dosage forms
- Describe common types of drug dosage forms
- Identify and categorize drugs on the bases of dosage forms
- Demonstrate how to convert weights and measures
- Demonstrate how to solve problems involving specific gravity, percent strength, weight in volume, weight in weight, and volume in volume
- Demonstrate how to perform dilution and concentration calculations

- Demonstrate use of milli-equivalents
- Identify common vitamins, minerals and electrolytes used in pharmaceutical service sectors in Ethiopia
- Identify and recommend common hair, beauty and cosmetic products

Teaching/learning methods

- Interactive Lectures
- Group discussions
- Cooperative learning/practical attachment
- Facility visit
- Individual and group work/exercise
- Case studies
- Demonstration
- Audiovisual

Teaching/learning materials

- Drugs based on the essential drug list
- Learning modules,
- Text books
- Audiovisual aids (LCD, computer, DVD)
- Work sheet
- Charts

Methods of assessment

- Written/oral examinations (quizzes, final examinations)
- Report writing
- Structured observation
- Individual and group assignments

Module Schedule

Week	Learning Activity	Required Reading / Assignment
Week one	<u>Day 1</u> <u>Interactive lecture (4 hrs.)</u> - Introduction to Pharmacy practice (Definition, History, Scope) <u>Skill Lab (4 hours)</u> - Pharmacy settings tour (hospital pharmacy, community pharmacy etc.) <u>Day 2</u> <u>Interactive lecture (4 hours)</u> - General principles of drug action (Definitions of basic terms, Drug sources, naming and classification) <u>Interactive lecture(2hrs)</u> - Dosage forms - Composition of dosage forms (active ingredients, excipients) - Types of dosage forms (Solid dosage forms, Semi-Solid dosage forms, Liquid dosage forms) <u>Practice (2 hours)</u> Dosage form demonstration <u>Day 3</u> <u>Recap on dosage forms (2hrs)</u> <u>Interactive lecture (4hrs)</u> - Routes of drug administration <u>Demonstration and group activity on routes of drug administration (2hrs)</u> <u>Day 4</u> <u>Interactive lecture (4 hrs.)</u> - Pharmacokinetic processes (ADME) <u>Demonstration (video show on ADME) (4hrs)</u> <u>Day 5</u> <u>Interactive lecture(4Hrs)</u> - Pharmacodynamics (common mechanism of drug action, agonists and antagonists, Efficacy, potency and Therapeutic index)	Learning Module National drug list National drug formulary Text books

	Group discussion on the activity given in the LM Demonstration or video show on agonist and antagonist (4hrs) Day 6 Guided reading of week 1 topics	
Week two	<u>Day 1</u> <u>Interactive lecture (4hrs)</u> - Adverse effects (Types, commonly encountered adverse effects) <u>Independent Reading (4hrs)</u> - Factors affecting drug action (Age, sex, weight, disease, pregnancy, nutritional status, genes, drug interaction) - Pregnancy category of drugs <u>Day 2</u> Reflection and discussion on factors affecting drug action (2hrs) Individual reading(4hrs) <u>Written Assessment 1(2hrs):</u> - on general principles of drug action <u>Day 3</u> <u>Interactive lecture (4 hours)</u> - ANS drugs (Introduction, Cholinergic Agonists, Cholinergic Antagonists) <u>Activity and discussion (4hrs)</u> <u>Matching cholinergic drugs with their indication</u> Discussion: - SEs and contraindications of cholinergic drugs and their management. - Case study <u>Day 4</u> <u>Interactive lecture (4hrs)</u> Adrenergic Agonists, Adrenergic Antagonists <u>Revision and activity: adrenergic drugs (4hrs)</u> <u>Day 5</u> <u>Interactive lecture (4hrs)</u> - CVS drugs - Overview of the circulatory system - Anti-hypertensive <u>Group discussion (4hrs)</u>	

	Moderated discussion on antihypertensive drugs classes <u>Day 6</u> <u>Independent reading</u>	
Week three	<u>Day 1</u> <u>Interactive lecture (4 hours)</u> - drugs for Heart Failure; Anti-anginal drugs; lipid lowering and Drugs for arrhythmia (list of drugs) <u>Interactive lecture (4 hrs.)</u> <u>Practice exercise on CVS drugs</u> <u>Day 2</u> <u>Independent reading(4hrs)</u> <u>ANS and CVS</u> <u>Written exam on ANS and CNS (3hrs)</u> <u>Day 3</u> <u>Interactive lecture (4hrs)</u> - Drugs acting on blood (Drugs for anemia, Anti-coagulants, anti-platelets and thrombolytics) <u>Group Activity (4hrs)</u> - Practice exercise on blood drugs <u>Day 4</u> <u>Interactive lecture (4hrs)</u> •GIT drugs • Anatomy and physiology • Drugs for acid peptic diseases • Emetics and Anti-emetics <u>Pharmacy setting attachment(4hrs)</u> <u>Day 5</u> <u>Interactive lecture (4hrs)</u> • Anti-diarrheal drugs • Drugs for constipation <u>Pharmacy setting attachment (4hrs)</u> <u>Day 6</u> <u>Written assessment</u>	
Week four	<u>Day 1</u> <u>Interactive lecture (4 hours)</u> CNS drugs	

	• Anatomy and physiology • Sedative hypnotics/anxiolytics • Mood stabilizers and Antidepressants <u>Interactive lecture (4hrs)</u> • Antipsychotics • Anti-seizure drugs/drug for epilepsy • Anesthetics (General, local) Day 2 <u>Interactive lecture (4hrs)</u> • Analgesics (opioids) • Narcotic and psychotropic act • Drugs for Parkinson disease <u>Independent reading (4hrs)</u> <u>Day 3</u> <u>Interactive lecture (4hrs)</u> Autacoids and Anti-inflammatory agents • Overview of prostaglandin and histamine • Anti-histamines <u>Pharmacy setting attachment (4hrs)</u> Day 4 <u>Interactive lecture (4hrs)</u> • Non-Steroidal anti-inflammatory drugs • Anti-gout <u>Pharmacy setting attachment (4hrs)</u> <u>Day 5</u> <u>Interactive lecture (4 hrs)</u> • Respiratory drugs (Introduction, Anti-asthmatics, Cough remedies) <u>Pharmacy setting attachment (4hrs)</u> <u>Visit pharmacy (community or hospital) to identify available Over the counter drugs</u> <u>Day 6</u> <u>Written assessment (4hrs)</u>	
Week five	Day 1 <u>Interactive lecture (4hrs.)</u> • Endocrine drugs (Introduction, Thyroid and anti-thyroid drugs (list drugs), Anti-diabetic drugs) <u>Group presentation</u> on their facility visit(4hrs) <u>Day 2</u>	

	<u>Interactive lecture (4hrs)</u> Contraceptives, Drugs used in obstetrics and gynecology (oxytocin, misoprostol, mifepristone, ergometrine, MgSO₄), Corticosteroids, drugs for erectile dysfunction <u>Group activity (4hrs)</u> • Hormonal contraceptives <u>Day 3</u> <u>Interactive lecture (4 hrs)</u> Chemotherapeutic agents • Overview of pathogenic organisms (bacteria, fungi, virus, protozoa, helminthes) • Principles of chemotherapy <u>Independent study (4hrs.)</u> Revision of disease causing microbes <u>Day 4</u> <u>Interactive lecture (4hrs)</u> • Antibacterial (Penicillin, Cephalosporin) • Sulfonamides and Trimethoprim <u>Independent study (4hrs)</u> Reading assignment on carbapenems, monobactams and vancomycin <u>Day 5</u> <u>Interactive lecture (4hrs)</u> • Summarize important points of the reading assignment given the previous day • Tetracycline, Aminoglycosides, Macrolide, Fluoroquinolones) <u>Interactive lecture (2hrs)</u> • Miscellaneous: Polymixin B, Clindamycin, chloramphenicol <u>Independent study (2hrs.)</u>	
Week 6	<u>Day 1</u> <u>Interactive lecture (4 hrs.)</u> • Anti-mycobacterial drugs (TB, Leprosy) <u>TB clinic visit (4 hrs)</u> <u>Day 2</u> <u>Interactive lecture (4 hrs)</u>	

	- Antifungal (Amphotericin B, Azoles (ketoconazole, fluconazole, miconazole, clotrimazole), Griseofulvin, Terbinafine, White field's ointment) Independent study (4hrs) <u>Day 3</u> Interactive lecture (4hrs) - Anti-viral (Acyclovir) - Anti-retroviral drugs - Introduction to HIV/AIDS, - NRTI: Zidovudine, Lamivudine, Emtricitabine, Tenofovir, Abacavir, - NNRTI: Nevirapine, Efavirenz, - Protease inhibitors: Ritonavir, Lopinavir, Atazanavir ART pharmacy Visit (4 hrs) <u>Day 4</u> <u>Interactive lecture(4hrs)</u> - Anti-protozoal (Amoebic agents, Anti-giardia drugs and Anti-malarial drugs) <u>Practical attachment (4hrs)</u> Hospital or community pharmacy <u>Day 5</u> <u>Interactive lecture (4hrs)</u> - Anthelmintic agents (Albendazole, mebendazole, Ivermectin, praziquantel, levamisole, Piperazine) - Anticancer drugs <u>Practical attachment (4hrs)</u> community or hospital pharmacy <u>Day 6</u> <u>Written assessment</u>	
Week 7	<u>Day 1</u> <u>Interactive lecture (4 hrs)</u> - Dermatological agents - Corticosteroids, Gentian Violet - Salicylic Acid, - Nitrofurazone, Fusidic acid, Benzyl benzoate, Crotamiton	

	<u>Practical attachment (4hrs)</u> Hospital or community pharmacy <u>Day 2</u> <u>Interactive lecture (4hrs)</u> • Vaccines and biological products ○ BCG vaccine ○ Rabies vaccine (antiserum) ○ Diphtheria, Pertussis vaccine ○ Yellow fever vaccine, Rota virus vaccine, Tetanus antitoxin ○ Measles vaccine, Hepatitis B vaccine, Meningococcal vaccine ○ Anti-Rho(D) <u>Clinic or pharmacy visit (4hrs)</u> To identify commonly used vaccines <u>Day 3</u> <u>Interactive lecture (4hrs)</u> • Vitamins ○ Water soluble vitamins ○ Fat soluble vitamins • Minerals (Zinc and calcium) • Electrolytes ▪ Normal saline ▪ Ringer lactate ▪ Ammonium chloride ▪ Magnesium chloride ▪ Oral rehydration solution ▪ Potassium chloride ▪ Sodium bicarbonate <u>Independent study (4hrs)</u> <u>Day 4</u> <u>Interactive lecture (8hrs)</u> Hair, beauty and cosmetic products • Shampoos, Conditioners, Paraffin oil, Vaseline • Skin powders, Sunscreen <u>Day 5</u> Practical attachment (4hrs) Visit to community pharmacy to see Hair, beauty and cosmetic products <u>Day 6</u> Written assessment	
Week 8	<u>Day 1</u> <u>Interactive lecture (4hrs)</u> Pharmaceutical calculations	

	• Weights and volumes of liquids • Weight in weights; weight in volume; volume in volume; volume in weight Practice exercise (4hrs) <u>Day 2</u> <u>Interactive lecture(4hrs)</u> • Density, specific gravity and specific volume Practice exercise (4hrs) <u>Day 3</u> <u>Interactive lecture (4 hrs)</u> • Ratio, proportion and percentages <u>Practice exercise (4hrs)</u> <u>Day 4</u> <u>Interactive lecture (4 hrs)</u> • Dilution, concentration and reconstitution Practice exercise (4hrs) <u>Day 5</u> <u>Independent reading</u>	
Week 9	<u>Hospital or community pharmacy attachment</u>	
Week 10	<u>Assessment</u>	